UNIVERSITY OF BIRMINGHAM

Literature Search on Elevated Blood Glucose Levels

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

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For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

Aggressive Research Intelligence Facility (ARIF)
West Midlands Health Technology Assessment Collaboration (WMHTAC)
Department of Public Health and Epidemiology
University of Birmingham
Birmingham
B15 2TT

arifservice@bham.ac.uk
0121 414 3166

1 Aims

The aim of this report was to address the following question submitted by the Driver Medical Group:

At what point does high blood glucose level become relevant in its effect on cognitive and/or visual function?

Further details are given in the request submitted by the Drivers Medical Group (Appendix 1 – Details of Request)

2 Background

At a recent Diabetes Mellitus Driver Medical Group Panel meeting the USA Waiver Scheme was considered.

The Panel was advised that in the USA individual States had previously applied different standards with regard to the ability of people with insulin treated diabetes to drive commercial vehicles. This differentiation had led to problems for drivers when wishing to drive inter- State. The waiver scheme enables individuals who do not meet licensing standards to supply medical information to demonstrate that they do not, in any event, pose a greater risk to road safety.[1] On scrutiny of these requirements it would appear that the assessment for insulin treated diabetes for commercial drivers is analogous to the C1 criteria that DVLA is currently applying.[1]

The Panel noted that in the USA waiver system advice was given not only for action to be taken when low blood glucose levels were recorded, but also in response to high blood glucose levels. Documents from the USA Department of Transport indicate that diabetic drivers of commercial vehicles granted a licence to drive under the waiver should stop driving if their blood glucose level exceeds 400mg/dl (approximately 22.2mmol/l) and only resume driving when it falls below this level.[2]

Subsequent discussion by the Driver Medical Group Panel raised concerns that the panel was not providing advice with regard to the problems of cognitive dysfunction associated with hyperglycaemia in the UK. It was considered important that the Panel should address this issue.

Further background information is given in the documentation supplied by the Drivers Medical Group contained in Appendix 1 – Details of Request.

Long term physical complications of hyper and hypoglycaemia are well documented as have the benefits of maintaining appropriate mean blood glucose and glycosylated haemoglobin (HbA1c). The functional effects (routine performance) of acute and chronic hyperglycaemia and hypoglycaemia in patients with insulin and non-insulin dependant diabetes are less well described.[3] Chronic effects relate to the continual decline in performance as a direct result of the cumulative effects of extreme blood glucose. Acute effects refer to transient reduction in performance, due to extreme blood glucose, that return to ‘normal’ once blood glucose

is normalised. Acute effects are of importance due to the periodic danger in which patients can be put whilst experiencing the effects.[3]
Whilst both acute and chronic effects could affect driver function, from the perspective of the DMGP in contemplating the provision of advice to diabetics regarding the effect of elevated blood glucose on their ability to drive at any given time, it is the acute effects which are more important.
Therefore, this report concentrates on identifying and assessing the evidence of the acute effects of hyperglycaemia on cognitive and visual function in adults with insulin and non-insulin dependant diabetes.

3 Methods

Briefly these were:

- To undertake a search for studies looking at the effects of acute hyperglycaemia on cognitive and/or visual function in adults with diabetes.
- To initially search for existing systematic reviews.
- To concentrate on prospective controlled primary studies in the absence of systematic reviews.
- To comment on the quality of such studies.
- To tabulate design characteristics and the findings of the studies.
- To undertake data analysis dependant on the evidence identified.

3.1 Searches

3.1.1 Existing Reviews.

Searches to identify existing systematic reviews on this topic were performed utilising the well-established ARIF search protocol (Appendix 3 – Search strategies)

3.1.2 Primary Studies

Searches were undertaken for primary studies in the Cochrane Library and Medline. The strategy was developed iteratively and modified accordingly. The search strategy in Medline employed multiple iterations of MeSH headings and text terms for hyperglycaemia, blood glucose and diabetes mellitus cross matched to terms for cognitive and visual function, in order to capture the most relevant literature.

Examples of the detailed search strategies can be found in Appendix 3 – Search strategies.

Searches were predominantly undertaken by an information specialist with additional input by a research reviewer. Both interacted to ensure searches were conducted appropriately.

Results of the searches were imported into bibliographic management software (Reference Manager, vr11; Thomson ISI ResearchSoft), duplicates were removed both electronically and manually.

An information specialist and a research reviewer scanned the search results for relevance based on information in the title and abstract. Studies that appeared to assess the effect of hyperglycaemia on cognitive/visual function were obtained in full.

Full copy articles were assessed for their match to the question being addressed (external validity) by a research reviewer using the criteria outlined below in order to obtain the most informative articles for further scrutiny and reporting.

Design:	Prospective or cross sectional study.
Population:	Adult diabetics (type 1/2/insulin/non-insulin dependant).
Exposure:	Acute hyperglycaemia ('naturally' occurring or induced).
Control:	Euglycaemia (in the same or different population to which hyperglycaemia occurred)
Outcome:	Results of tests attempting to measure cognitive function and/or visual function
Exclusion:	Studies on children, non-diabetics, chronic hyperglycaemia, solely on hypoglycaemia. Studies with no obvious control. Studies where the outcome was solely perception of glycaemia or mood.

The reference lists of the most relevant articles were also checked in order to identify further relevant articles.

Relevant information on the design and conduct of the selected studies was tabulated along with information on relevant outcomes.

3.1.3 Driving Specific Literature

Ad hoc internet searches were conducted to identify relevant driving specific literature using data sources such as the National Transport Laboratory (TRIS), Transport Research Laboratory (TRL) and the Highways Agency.

4 Results

4.1 Reviews Identified

No relevant systematic reviews were identified.

Of the narrative reviews identified the most relevant is probably that by Cox *et* al 2002, which contains a small section on the acute effects of hyperglycaemia on cognitive function in type 1 and type 2 diabetics as well as sections on chronic effects of hyperglycaemia and the acute and chronic effects of hypoglycaemia on this parameter.[3] The acute hyperglycaemia sections rely on data from the studies by the same authors and therefore these primary studies rather than this review should be read; see data below from Cox *et al* 1995.[4]

4.2 Primary Studies Identified

From the searches for primary studies, over 380 articles were identified as being potentially of relevance to this report. Of these, 11 articles from 10 studies were directly relevant and these are outlined in detail in Table 1.[4-14] All the studies were identified from the searches of Medline and no additional studies were identified through citation checking of these articles.

There were a series of studies that did not make this final stage as they did not address cognitive or visual function, however they did measure patient perception of their blood glucose level and/or mood under euglycaemia or hyperglycaemia. Whilst not directly relevant to this report they may be a starting point with which to consider some aspects of the wider issues around driving with diabetes.[15-19]

4.2.1 Experimental Studies

Turning to the relevant studies, 9 of the 10 were of an experimental balanced crossover design where a small group of diabetic patients had blood glucose levels artificially adjusted and maintained at one or more hyperglycaemic level whilst functional studies were undertaken. Each patient acted as their own control with outcomes recorded at euglycaemic levels acting as the baseline with which to assess the effect of hyperglycaemia. Of the 9 studies of this type:

- 8 studies investigated type1/insulin dependant diabetics[5-12] and the other study type 2 diabetics.[13]
- 6 measured some form of cognitive function[5,7-10,13] and three visual function[6,11,12]
- All had small sample sizes (mean n≈19, range n=10-44).
- Patient election was poorly described or not described at all in most studies and this impacts on the generalisability of findings.
- 3 described the order at which patients experienced the glycaemic levels as randomized, although the randomization process was not described.[5,6,13]
- Patients were blinded to the glycaemic levels in 7 studies[5-10,13] and investigator/outcome assessor were blinded in 4 of these studies[5,7,9,10], however the method of blinding is not described in any.

- Euglycaemic blood glucose levels utilised ranged from 4.5 to 6.7mmol/l and hyperglycaemic levels 13.9 to 21.1mmol/l. See Figure 1 for the levels utilised by individual studies.
- 6 studies performed all measurements in one session[7-12] and 3 in separate sessions between one week and one month apart.[5,6,13]
- Multiple outcome measures were used across the studies to assess cognitive function and/or visual function. Cognitive function outcome measures included: Recall of sequences (numbers/letters/words), reading and mathematical tests, reaction times (visual and/or aural stimulus with 0, 1 and 2 choice decision making), visual/motor control (tracking a moving object), sensory/motor control (trail making), verbal fluency (word generation), visual contrast sensitivity, visually evoked potentials, visual pathway function (colour discrimination). Very few of the studies described the tests in detail. It was unclear if any of the tests had been validated as measures of cognitive or visual function.

From the studies on type 1/insulin dependant diabetes, lack of full description of populations, study designs and outcome measures hampers drawing meaningful conclusions across the studies even where it appears that similar outcomes are being measured.

General themes are apparent though. Very few statistically significant differences were observed for cognitive function assessment between euglycaemia and the hyperglycaemic levels utilised in the studies. This is in contrast to those studies that measured cognitive function in euglycaemia and hypoglycaemia where statistically significant differences were more often observed and were typically larger than those seen in hyperglycaemia. Where a statistically significant finding was observed for cognitive function in one study a non-significant finding in a similar test was observed in another study (i.e. trail making was found to be significantly impaired with hyperglycaemia in type 1 diabetics in Draelos et al at 14.4 and 21.1mmol/l but not impaired in Hoffman et al 16.7mmol/l).[5,7]

With regard to the effect of hyperglycaemia on visual function, no statistically significant findings were found for visually evoked potentials and visual pathway function. One study seems to suggest there is a significant difference in contrast sensitivity on induced hyperglycaemia. This information is taken from an English abstract to a German language paper and until a full translation of the paper is obtained this finding should be treated with caution.[11]

With regard to type 2 diabetes, the only study (Sommerfield et al 2004) that undertook hyperglycaemic clamping investigations found no statistically significant impairment of overall immediate and delayed memory.[13] Significant impairment of information processing was observed. Reaction time was not. Some measures of attention underwent small but significant deterioration.[13] It is worth noting that the type 2 diabetics in this study had a much greater mean age than the type 1 diabetics enrolled in the other clamping studies. Furthermore this study was subject to the same methodological and reporting limitations as the type 1 studies.

4.2.2 Cross Sectional Study

The remaining relevant study (Cox et al 2005) was a cross sectional survey of three diabetic groups.[4] Two groups had type 1 diabetes and the other type 2. The survey was meant to get a 'real world' effect of hyperglycaemia on cognitive function. The sample sizes for each of the two type 1 studies was about 100 and thus much greater than in the experimental studies. Patient selection, blinding and some other methods are not fully described. Patients were given a hand held computer containing a range of cognitive function tests and asked to complete the tests at least 50 times over a four week period prior to measuring and recording their blood glucose level on each occasion. There was some variation in the tests given to each of the groups and some, but not necessarily robust, attempt was made to blind subjects by trying to ensure that the functional tests were completed prior to glucose measurement. The tests included mental subtraction/addition, word generation, four choice reaction time. Results were analysed by blood glucose level at each testing session in bands 6.1-8, 8-10, 10-12.5, 12.5-15, >15mmol/l. It is unclear if these bandings were chosen *a priori*. Statistical analysis was conducted comparing >15mmol/l band to the 6-8mmol/l band. Some statistical attempts were made to account for the fact that each patient would have multiple entries in each band. For analysis of data from type 1 diabetics the number of data points in each of the compared bandings were relatively similar.

Given its methodology this study is open to more bias and confounding than those of an experimental design and its findings should also be treated with a degree of caution. However, it has merit in that it attempts to assess the effect of acute hyperglycaemia over multiple assessments, with a larger sample size, longer time frame and in a more real world environment.

In both type 1 diabetic groups there was statistically significant deterioration in mean mental subtraction time between euglycaemia and hyperglycaemic band (>15mmol/l). In one group there was a statistically significant increase in the mean number of errors on this test. Statistically significant fewer mean number of words were generated when hyperglycaemic in the only type 1 group to be given a word generation test. All other outcomes measured in type 1 patients were not statistically significant.

In type 2 diabetics statistically significant fewer mean number of words were generated in a word generation test whilst hyperglycaemic, as well as slower mental subtraction, increased subtraction errors and more errors on serial addition tests. For all the other outcomes assessed there were no statistically significant differences between euglycaemia and hyperglycaemia (>15mmol/l).

4.2.3 Driving Performance

One of the experimental studies (Hoffman et al) attempted to assess the effects of hyperglycaemia on driving ability of type 1 diabetics using a simulator.[7] No effects of hyperglycaemia were noted (whereas hypoglycaemia did have an effect on driving performance). However as driving performance was only measured on ten of the 18 patients in the study, the findings should be treated with some caution.

No driving specific information on the effects of hyperglycaemia on performance was identified other than in the study by Hoffman et al.[7]

5 Conclusion

It is evident from the studies above that whilst hyperglycaemia appears to have some effect on certain measures of function in some type 1 and type 2 diabetics this effect is not uniform i.e. the same outcome is not adversely affected in all studies (which measure it) and the consistency of any effect is unclear, as most of the studies measure outcomes in a single euglycaemic or hyperglycaemic session. When differences are observed between euglycaemia and hyperglycaemia the magnitude of any detriment tends to be small, and smaller than that seen between euglycaemia and hypoglycaemia. Furthermore there are many outcomes which are not affected by hyperglycaemia in the studies.

To draw meaningful conclusions from the above studies with regard to the effect of hyperglycaemia on cognition is almost impossible given the limitations of the study designs employed, the small sample sizes, the absence of some information in the reporting of the studies, the heterogeneity of outcome measures utilised and the differing tools (and lack of demonstration of validation of the tools) used to measure them. This is without even considering the heterogeneity of the findings themselves.

We found no studies assessing the effect of rate of change of blood glucose level (euglycaemia to hyperglycaemia) on cognitive and/or visual function.

A further issue for the DMG is even if there was a demonstrable effect of hyperglycaemia on cognitive or visual function, to extrapolate this to suggest a detrimental effect on driving performance is difficult.
One study has attempted to measure driving performance under euglycaemic and hyperglycaemic conditions, however the findings cannot be relied upon as only about half the sample were assessed for this outcome. In order to obtain a more definitive answer, it might be pertinent for the DMG to place the undertaking of a similar study on the transport research agenda or to encourage in future studies the utilisation of tests of cognitive function which have been validated as correlating to ability to drive.

In summary, there is no consistent evidence from the studies identified in this report to suggest that cognitive and/or visual function are significantly impaired with acute hyperglycaemia although in some individuals with diabetes (type 1 and type 2) some measures of cognitive function might be impaired. At the levels of hyperglycaemia assessed in the studies, this impairment appears to be smaller and more variable than, the more consistent and general effects measured in diabetics undergoing hypoglycaemia. At present there is insufficient evidence to suggest an upper blood glucose level beyond which cognitive and/or visual function will be affected to such a degree that diabetics should cease driving until blood glucose falls. No evidence was found for the threshold of 400mg/dl (≈22.2mmol/l) recommended by the USA Department of Transport.

5.1 Limitations of this report

This is not a systematic review but a rapid assessment of relevant literature

Although the search strategies were broad and comprehensive for both systematic reviews and primary studies, it cannot be guaranteed that relevant studies were not omitted. A limitation is that searches for primary studies were only conducted in Medline and the Cochrane Library and not Embase. However, citation checking of relevant articles did not identify any further studies.

Table 1 Characteristics and Results of Studies on the Effect of Hyperglycaemia on Congitive and Visual Function in Adults with Diabetes

Study	Design	Population	Intervention/Comparator	Outcomes/Tests	Results*	Comments
Holmes et al 1983[8]	Experimental balanced crossover	Type 1 diabetics N=12 (6 male) .	Patients were artificially established at three concentrations of blood glucose (60mg/dl (hypo), 110 mg/dl (normal), 300 mg/dl (hyper)) using a glucose/insulin infuser. The sequence was 'balanced'. A 1.5 hr period was used to establish the BG level and then the level maintained for 30 min of testing. The sequences were administered serially with a total study duration of 6 hrs/patient. Patients were blinded to the glucose levels and sequence	The following were assessed in patients in a random order. Memory: digit supraspan (9 digit sequence), verbal learning (15 word sequence) Attention: matching figures, reaction time. Visual spatial: copying geometric shapes Academic: Reading test (Nelson Denny), mathematics (computation of maths facts).	No significant effects were found for: visual perception, (matching figures, copying complex geometry), academic tasks (maths, reading comprehension), memory (word recall). Reaction time may be slowed.	Little patient information is given. Patient selection is not described. Balancing of glucose sequence, blinding and other methods are not fully described. Unclear if outcome assessors were blinded to glucose level. Difficult to adequately extract findings for some outcomes.

*Only findings relating to the effects of hyperglycaemia are presented in the table. Many of the articles also present findings on the effects of hypoglycaemia.

Study	Design	Population	Intervention/Comparator	Outcomes/Tests	Results*	Comments
Holmes et al 1986[9]	Experimental Balanced Crossover	Type 1 diabetic males (mean duration 8yrs 2mnths (rng: 6mths-19yrs)) Age 18-35 yrs (21.3 mean) N=24	Patients were artificially established at three concentrations of blood glucose (55mg/dl (hypo), 110 mg/dl (normal), 300 mg/dl (hyper)) using a glucose/insulin infuser. The sequence was 'balanced' and unknown to patient and investigator. A 2.5 hr period was used to establish the BG level and then the level maintained for 30 min of testing. The sequences were administered serially with a total study duration of 9 hrs/patient.	Simple motor responding (Finger tapping task) Sensory perception (tachistoscopic presentation of letters) Complex/sensory motor function (visual reaction time with 0, 1 and 2 step decision making))	For hyperglycaemia there were no statistically significant differences for any outcome from testing under normoglycaemia.	Patients had to have sufficient control to avoid ketoacidosis and duration of disease longer than 6 months. Pts with overt diabetic neuropathy were excluded from the study. All participants had at least average intelligence. Patient selection, balancing of glucose sequence, blinding and other methods are not fully described. Results tend to concentrate of hypo rather than hyperglycaemia.
Holmes 1987[10]	Experimental, balanced crossover	Type 1 diabetic males N=16	Patients were artificially established at three concentrations of blood glucose (55mg/dl (hypo), 110 mg/dl (normal), 300 mg/dl (hyper)) using a glucose/insulin infuser. The sequence was 'balanced' and unknown to patient and investigator. A 2.5 hr period was used to establish the BG level and then the level maintained for 30 min of testing. The sequences were administered serially with a total study duration of 9 hrs/patient.	Neuropsychological skills: motor responding (finger taps) to more complex mental responding (reaction time decision making) Auditory reaction time (simple RT, with 0, 1 and 2 choice decision making)	No significant difference between normal and hyperglycaemic states for simple auditory reaction time, 0,1 and 2 choice decision making, and finger tap test. Ad hoc sub group analysis undertaken based on reaction time to one step decision making findings of hypo compared to normal blood glucose levels was undertaken. This should be treated with caution.	Patients had to have no overt diabetic neuropathy or neuropathy. All participants had at least average intelligence. Patient selection, balancing of glucose sequence, blinding and other methods are not fully described. Similar to Holmes et al 1986 but with auditory rather than visual stimuli. Ad hoc subgroup group analysis should be treated with a degree of caution.

*Only findings relating to the effects of hyperglycaemia are presented in the table. Many of the articles also present findings on the effects of hypoglycaemia.

Study	Design	Population	Intervention/Comparator	Outcomes/Tests	Results*	Comments
Hoffman et al 1989[7]	Experimental Balanced Crossover	Type 1 diabetics (mean duration 7.7±1.6 years) Age 22-35yrs (mean 29.3±1.2 yrs) N=18 (8 males)	Patients were artificially established at three concentrations of blood glucose (50mg/dl (hypo), 100 mg/dl (normal), 300 mg/dl (hyper)) using a glucose/insulin infuser. The sequence was 'balanced' and unknown to patient and investigator. A 1 to 2 hour period was used to establish the BG level and then the level maintained for 30 min of testing. The sequences were administered serially with a total study duration of 8-10 hrs/patient	Sensory, motor and cognition tests of increasing difficulty: Motor speed: reaction time to visual cue. Visual/motor control: tracking a point on a rotating object Sensory motor/cortical functioning: trail making tests Driving test on a simulator. (10/18 patients only)	No statistically significant effects from normal glycaemic control were observed during hyperglycaemia (hypoglycaemic effects that were statistically significant were: complex trail making and point tracking)	Patients demonstrated no neuropathy or retinopathy. Patient selection balancing of glucose sequence, blinding and other methods are not fully described. Results for driving ability in a simulator should be treated with caution as only 10/18 patients were measured for this test.

*Only findings relating to the effects of hyperglycaemia are presented in the table. Many of the articles also present findings on the effects of hypoglycaemia.

Study	Design	Population	Intervention/Comparator	Outcomes/Tests	Results*	Comments
Draelos et al 1995[5]	Experimental Randomised Crossover	Type 1 diabetes (mean duration 8.7 ± 3.5yrs) Age: 29±8yrs N=20 males/ 22 females	After initial assessment, patients were subjected to two sessions one month apart of glucose clamp step wise from euglycaemia (8.9mmol/l) to hyperglycaemic (14.4 and 21.1mmol/l) or hypoglycaemic clamp (5.6 and 2.2mmol/l) in a random order. Patients were maintained at each level for 1 hour with outcomes measured during the final 25 minutes. The patients and outcome assessors were blinded to glucose levels.	Complex/sensory motor function (visual reaction time, with 0 and 1 choice decision making) Digit vigilance test (test of attention over time whilst focussing on detail) Combined test of mental flexibility/ visual conceptual and visual spatial skills (trail making) Verbal memory (word recall) Digital sequence learning Verbal fluency (generate words beginning with a given letter)	No statistically significant difference were seen in the mean test scores for simple reaction times, choice reaction times, digital vigilance (% errors), serial digit learning compared to baseline at either 14.4 or 21.1mmol/l. Statistically significant deterioration was found at both levels in digital vigilance (number of items) although this change was quite small; trail making. Verbal fluency was slightly improved at 21.1mmol but not at 14.4mmol/l. Statistically significant deterioration was seen in all parameters for hypoglycaemia at 2.2mmol/l.	Patients had to be adults less than 44yrs old have had diabetes for 3-14yrs have no neuropathy or retinopathy and not been pregnant in the previous two yrs. Patient selection, randomisation, blinding and other methods are not fully described
Weinger et al 1995[14] *Report of more outcomes from Draelos et al 1995 above*	See above	See above	See above	Mood Perception of blood glucose level	See paper - no need to state here as not directly relevant to this report	See above

*Only findings relating to the effects of hyperglycaemia are presented in the table. Many of the articles also present findings on the effects of hypoglycaemia.

Study	Design	Population	Intervention/Comparator	Outcomes/Tests	Results*	Comments
Sommerfield et al 2004[13]	Experimental randomised 'counterbalanced' crossover	Type 2 diabetics (duration 5.9yrs (rng:2.8-11.2yrs)) Median age: 61.5yrs (range 53.1-72.0) N=20 (12 males)	After initial assessment, patients were subjected to two sessions at least two weeks apart of hyperinsulinemic glucose clamp. Blood glucose was either maintained at 4.5mmol/l or raised over a 20 minute period to 16.5 mmol/l. Once maintained at the desired level for 10 minutes a testing period of 80 minutes was begun. The patients were blinded to which arm of the study was being undertaken on each occasion..	Cognitive Function: *Information processing* (trail making, digit symbol test, reaction time rest) *Test of memory* (verbal memory, visual memory, working memory) *Test of attention* (test of everyday attention) Mood Questionnaire of mood (energetic arousal, tense arousal and hedonic tone) devised by University of Wales.	*Information processing:* Statistically significant impairment of trail making, digit symbol test and four choice reaction time. Simple reaction time was not significantly impaired. *Test of memory:* No significant effects on immediate or delayed memory. Statistically significant impairment of two measures of working memory (digit span backwards, letter/number sequencing) but not the third (digit span forwards). *Test of Attention* Some measures of attention show small but significant deterioration with hyperglycaemia. Other measures appear to show a trend to deterioration that is not statistically significant. There seems to be a general trend towards longer times to complete tasks with hyperglycaemia. *Mood* Statistically significant decrease in happiness and alertness and an increase in agitation with hyperglycaemia.	Patients were excluded if they had evidence of microvascular disease (except background retinopathy). No other inclusion/exclusion criteria are specifically mentioned. Three patients were insulin dependant. Patient selection, randomisation, 'counterbalance', blinding and other methods are not fully described. Investigators/outcome assessors do not appear to have be blinded to the blood glucose level.

*Only findings relating to the effects of hyperglycaemia are presented in the table. Many of the articles also present findings on the effects of hypoglycaemia.

Study	Design	Population	Intervention/Comparator	Outcomes/Tests	Results*	Comments
Cox et al 2005[4]	Repeat sampling 'cross sectional survey'	Three populations were studied. Study 1:Type 1 diabetes Duration: 19.7±9.9(2-46) Age: 37.5±0.9 (23-39)yrs N=105 (40 males) Study 2: Type 2 diabetes Duration: 10±9(1-35) Age:50±11(28-75) N=34 (19 males) Study 3: Type 1 diabetes Duration: 20.2±10.7(1-52) Age: 39.4±10.4(25-61) N=91 (39 males)	Patients were given a hand held computer containing a battery of cognitive function tests which they were asked to complete 3 to 4 times per day over 4 week period for a total of 50 trials (states 70 in abstract),. The tests were to be performed prior to routine blood glucose testing to ensure patients were blind to the level. Steps were taken to try to ensure this occurred. Data collectors were also blind to hypothesis under investigation. Study 1 was repeated 5 months after the first month of measurements to test reliability.	Study 1: Three cognitive motor tests: Thinking of as many words beginning with a given letter in 30sec. Ten mental subtraction problems (one digit number from a three digit one). Four choice reaction time. Study 2: As study 1 except using a different make of computer and with a two levels of a paced serial addition test instead of the reaction time test. Study 3: Ten mental subtraction problems (to reduce the test burden on the patient compared to study 1 & 2.	Results were analysed by blood glucose level in bands corresponding to: 6.1-8, 8-10, 10-12.5, 12.5-15, >15mmol/l Study 1: Blood Glucose >15mmol/l was associated with slower performance on some psychomotor tasks. Statistically significant fewer words retrieved and slowed mental subtraction. All other outcomes were not statistically significant for this or any other blood glucose band. E.g. no effect on choice reaction time at >15mmol/l. Study 2: Blood Glucose >15mmol/l was associated with slower performance on some psychomotor tasks. Statistically significant fewer words retrieved, slowed mental subtraction, increased subtraction errors, and more addition errors on the serial addition test. All other outcomes were not statistically significant for this or any other blood glucose band Study 3: Blood Glucose >15mmol/l was associated with slower mental subtraction time and increased number of errors. All other outcomes were not statistically significant for this or any other blood glucose band.	There are three studies of similar design on two different populations described in this article. Patient selections, blinding and some other methods are not fully described. Unclear why the blood glucose level bandings were chosen for the analysis. P value for significance lowered to <0.01 to account for multiple entries for each patient in each banding. Samples from study1 at initial month and repeat testing at 5 months were pooled. ?appropriateness of this. Analysis was undertaken based on the number of patients who had significant disruption to one or more test compared at >15mmol/l compared to 6-8mmol/l.

*Only findings relating to the effects of hyperglycaemia are presented in the table. Many of the articles also present findings on the effects of hypoglycaemia.

Study	Design	Population	Intervention/Comparator	Outcomes/Tests	Results*	Comments
Martinelli et al 1992[12]	Experimental 'before and after'	Insulin dependant diabetes. Duration mean 11.7 (2-30)yrs Age 31±3yrs (19-48yrs) N=10 (6 males)	Patients had their blood glucose level raised over one hour from 120 mg/dl and then maintained at 250mg/dl for 180 minutes.	Visually evoked potentials	No significant change in any of the neurophysical parameters measures of induction and maintenance of hyperglycaemia.	2 patients had retinal evidence of background diabetic retinopathy. Patient selection not fully described.
Hardy et al 1995[6]	Experimental randomised crossover	Type 1 diabetics (mean duration 9±4yrs) Age 28±7yrs N=10	Patients were artificially established at three concentrations of blood glucose (2.5mmol/ll (hypo), 5mmol/l (normal), 14.4mmol/l (hyper)) using a glucose/insulin infuser, on three separate occasions at least one week apart, in a random order. After 1-2 hours of stabilisation outcomes were measured. The sequence was unknown to patient.	Visual pathway function (Farnsworth Munsell 100 hue test)	No statistically significant difference in visual pathway function at different glucose levels.	Patients had no evidence of microvascular disease. Patients were aretinopathic. Limited other patient information. One patient only performed the hypoglycaemia study and one did not perform the hypoglycaemia study. Patient selections, randomisation of sequence, blinding and other methods are not fully described.
Mangouritsas et al 1995[11] *Article in German, abstract in English. Information taken form abstract.*	Experimental 'before and after'	Insulin dependant diabetes Duration 11.4±7.3yrs Age 32±8.2yrs N=20 (9 males)	Patients had their blood glucose level raised from 116±14mg/dl to 274±mg/dl	Contrast sensitivity	Visual acuity remained stable during hyperglycaemia. Statistically significant in mean contrast sensitivity scores between euglycaemia and hyperglycaemia.	Information taken from the abstract and therefore should be treated with some degree of caution. There is also more information in the full paper but required translation

*Only findings relating to the effects of hyperglycaemia are presented in the table. Many of the articles also present findings on the effects of hypoglycaemia.

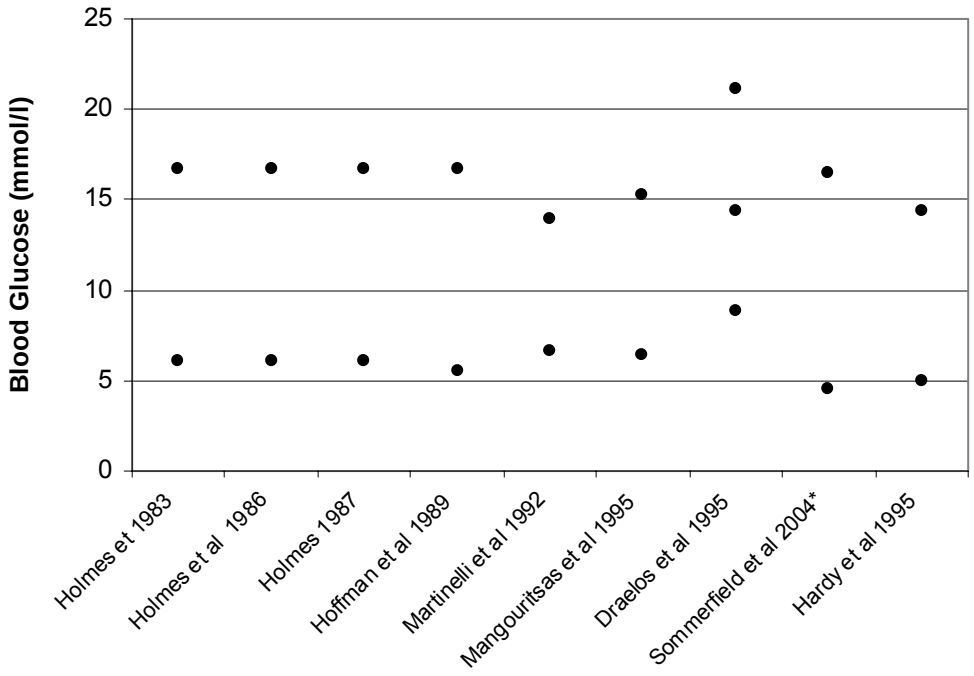

Figure 1 Blood Glucose Levels Utilised in Glucose Clamp Studies on Effects of Hyperglycaemia

**Undertaken of Type 2 diabetics. All other studies were on Type 1 / Insulin dependant diabetics.*

6 References

6.1 Main References

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7 Appendices

7.1 Appendix 1 – Details of Request

ARIF REQUEST FORM

7.2 Date of Request

01 / 12 / 2005

Lead Medical Adviser Issuing request	Name – Dr Delyth Sheppard Secretary to Diabetes Mellitus Panel
7.2.1 Contact details	Drivers Medical Group DVLA Sandringham Park Swansea Vale Llansamlet Swansea SA7 OAA [redacted]

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

We need to know at what point does a high blood glucose level become relevant in its effect on cognitive and/or visual function.

2. Please give a background to the question. Why has DMG raised this problem?

At a recent Panel meeting, after considering the U.S. Waiver Scheme, discussions raised concerns that the Panel was not providing advice with regard to the problems of cognitive dysfunction associated with hyperglycaemia.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background nformation on the *options* and *issues*, which might be important for the problems, you describe.

(a) American Diabetes Association, Transportation Legislation – News Release

(b) Federal Register, Vol 68, No. 170, September 2003

(c) Federal Motor Carrier Safety Administration

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel member.

Professor Brian M Frier (Chairman)
BSc Ed MD FRCP
Consultant Physician and Diabetologist
Department of Diabetes
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH 16 4SA
[redacted]

Dr A E Gold (Panel Member)
BSc Ed MD MRCP
Consultant Physician, Diabetologist and Endocrinologist
Wards 27/28
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZN
[redacted]

5. What is the nature of the target population of the issue detailed above? E.g. age, profile, vocational drivers, young drivers, other co-morbid features.

Age profile: all ages
Drivers: vocational and ordinary (car)

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

We want to advise drivers at what high level of blood glucose they should not consider driving, as we already advise regarding low blood glucose reading. This would aid individual risk assessment and could affect licensing decisions.

7.2.2 What is the latest date that an ARIF response would be of value

01 / 03 / 2006

Please either:

7.2.3 Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: [redacted]

Post to:-

Dr David Moore
Senior Research Reviewer and Analyst
Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration
Department of Public Health
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Please ring 0121 414 3166 or 6767 if you have any queries, or you want to check the progress with your request.

7.3 Appendix 3 – Search strategies

7.3.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

(Feb 2005)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

A. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

B. ARIF Database

- An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

C. NHSCRD (WW Web access)

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

D. Health Technology Assessments and evidence based guidelines(WW Web access)

- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes (NCCHTA work pages:www.ncchta.org/nice/)
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Co-ordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex STEER Reports
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre
- SIGN (Scottish Intercollegiate Guidelines Network)

E. Clinical Evidence

F. Bandolier

G. TRIP Database

H. Bibliographic databases

- Medline - systematic reviews
- Embase - systematic reviews
- Other specialist databases.

I. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (&MTRAC) and West Midlands Drug Information Service (url: www.ukmicentral.nhs.uk) for any enquiry involving drug products

7.3.2 Primary studies protocol

Database: Ovid MEDLINE(R) <1966 to January Week 3 2006>
Search Strategy:
---
1 exp Hyperglycemia/ (13203)
2 (glucose adj3 estimat$).ti,ab. (1011)
3 Cues/ (12925)
4 recognition.mp. (132046)
5 or/2-4 (144339)
6 1 and 5 (134)
7 from 6 keep 1-134 (134)

Database: Ovid MEDLINE(R) <1966 to January Week 3 2006>
Search Strategy:
---
1 (blood adj2 sugar$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4469)
2 (blood adj2 glucose).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (94095)
3 exp Blood Glucose/ (84571)
4 or/1-3 (95737)
5 control$.ti,ab. (1370300)
6 exp Self Care/ or exp Blood Glucose Self-Monitoring/ or self monitoring.mp. (23204)
7 aware$.ti. (5448)
8 recogni$.ti. (36337)
9 monitor$.ti. (49022)
10 or/5-9 (1469033)
11 4 and 10 (31584)
12 vision.mp. (66696)
13 visual.mp. (188811)
14 sight.mp. (3822)
15 eyesight.mp. (254)
16 cognit$.ti,ab. (79659)
17 or/12-16 (295159)
18 11 and 17 (575)

19 limit 18 to (humans and "therapy (specificity)") (85)
20 limit 18 to (humans and "diagnosis (sensitivity)") (145)
21 or/19-20 (222)
22 hyperglycemia.mp. or exp Hyperglycemia/ (21983)
23 hyperglycaemia.mp. (3774)
24 or/22-23 (24519)
25 21 and 24 (17)
26 18 and 24 (57)
27 limit 26 to humans (52)
28 from 27 keep 1-52 (52)

Database: Ovid MEDLINE(R) <1966 to January Week 3 2006>
Search Strategy:
---
1 exp Hyperglycemia/ (13203)
2 exp Diabetes Mellitus/ (182038)
3 exp "Quality of Life"/ (50200)
4 1 and 2 and 3 (32)
5 from 4 keep 1-32 (32)

Database: Ovid MEDLINE(R) <1966 to January Week 1 2006>
Search Strategy:
---
1 (blood adj glucose adj3 level$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7911)
2 change$.ti. (221509)
3 alter$.ti. (98017)
4 dip$.ti. (43660)
5 2 or 3 or 4 (360761)
6 1 and 5 (349)
7 (blood adj glucose).ti. (4196)
8 5 and 7 (217)
9 hypergly$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (25950)
10 8 and 9 [8 and 9 as keyword] (38)
11 limit 10 to humans (23)
12 from 11 keep 8,14 (2)

Database: Ovid MEDLINE(R) <1966 to January Week 3 2006>
Search Strategy:
---
1 HbA1C.mp. (5092)
2 exp Hemoglobin A, Glycosylated/ or exp Blood Glucose/ (89880)
3 1 or 2 (91510)
4 cognit$.tw. (79659)
5 visual.mp. (188811)
6 exp Vision/ or vision.mp. (101084)
7 eyesight.mp. (254)
8 sight.mp. (3822)
9 or/4-8 (295732)
10 3 and 9 (1040)
11 4 or 5 (260472)
12 3 and 11 (927)
13 hyper$.mp. (854949)
14 12 and 13 (195)
15 10 and 13 (224)
16 limit 15 to (humans and "diagnosis (specificity)") (0)
17 limit 15 to (humans and "diagnosis (sensitivity)") (62)
18 limit 15 to (humans and "therapy (optimized)") (41)
19 17 or 18 (100)
20 1 and 9 (127)
21 13 and 20 (35)
22 19 or 21 (117)
23 from 22 keep 1-117 (117)