Diabetes and driving

Performance, decision making and legal aspects

Alexander Daniël Maarten Stork

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Diabetes and driving

Performance, decision making and legal aspects

Diabetes en autorijden

Rijvaardigheid, besluitvorming en juridische aspecten

(met een samenvatting in het Nederlands)

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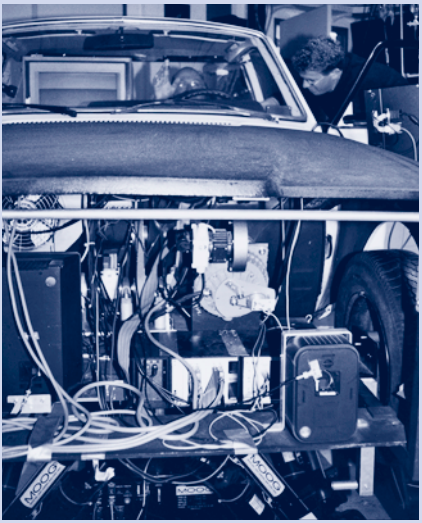

Alexander D.M. Stork

In modern society, mobility has become increasingly important. A growing number of kilometres are travelled, many of which are driven by car. In the Netherlands, for example, the number of kilometres travelled has increased from 144.2 milliard in 1985 to 190.9 milliard in 2003[1]. A large proportion of this increment can be attributed to transportation by car (from 107.0 to 146.1 milliard)[1]. Moreover, there is a significant shift in the age distribution in western societies towards higher age[2]. Additionally, older persons also show an increased mobility in general, and an increased number of kilometres driven by car in particular[3].

Simultaneous to the increasing mobility, the incidence of both type 1[4-6] and type 2 diabetes[7-9] is mounting throughout the world. It is hypothesised that the former increases due to infectious, nutritional or environmental changes[4], whereas the latter is most probably related to changes in obesity and lifestyle[10,11]. After the DCCT[12] and the UKPDS[13], which showed that diabetic complications are reduced with tight glucose control, management of diabetic patients is progressively aiming at near-normoglycaemia. Consequently, the rate of hypoglycaemia has markedly increased. This almost inevitably results in higher rates of hypoglycaemia unawareness, currently affecting approximately 25% of patients with type 1 diabetes[14-16]. Although the incidence of severe hypoglycaemia is lower in type 2 diabetes[16-18], it may approach the incidence in type 1 diabetes[17,19], when type 2 diabetes advances and glucose counter regulation fails[20,21].

This thesis is sited at the cutting edge of increasing automobile mobility and changes in incidence and treatment of diabetes. Driving a car is a complex task, in which technological, psychological and physical factors may play a role. Most drivers consider themselves better drivers than average[22,23]. Traffic can arouse various, often intense, emotions, and many people have unambiguous opinions about traffic. This may also be the case because in traffic certain risks are involved for both the driver and other participants. Throughout the world restrictive legislature concerning diabetic drivers has been issued, and currently, the debate on the issue of traffic safety of patients with diabetes mellitus is rising on national and international political as well as scientific levels. Generally, (professional and public) opinions as well as legal restrictions regarding diabetes and driving are mainly prompted by the impending danger of hypoglycaemia during driving. Opinions may also be influenced by anecdotal reports and by media attention to road traffic accidents where diabetic patients, possibly hypoglycaemic, are involved. Recently, in the United States of America, one such event has even resulted in a National Transportation Safety Board Public Hearing on Medical Oversight of Non-Commercial Drivers (March 3, 2003)[24].

Outline of the thesis

It appears that one must be very cautious as to form opinions and make policies based on the available scientific evidence rather than on isolated reports, particularly because an increasingly large number of patients is involved. Therefore, in this thesis, in *Chapter 2* the current state of affaires regarding diabetes and driving is reviewed, including the further studies needed to elucidate the relationship between diabetes and driving. A number of these further studies are described in *Chapters 3, 4 and 5*. In

Chapter 3 a study is described concerning driving performance of type 1 diabetic subjects with normal and with impaired hypoglycaemia awareness, and the effect of moderate hypoglycaemia on driving performance. An identical study in type 2 diabetic subjects with normal hypoglycaemia awareness is described in *Chapter 4*. The decision to initiate driving or to take appropriate action during driving when hypoglycaemic is evaluated in *Chapter 5*. In diabetes research in general, and in research on the relationship between diabetes, hypoglycaemia, hypoglycaemia awareness and driving in particular, methodology is important. Methodological studies are described in *Chapters 6 and 7*. For various reasons, the establishment and maintenance of euglycaemia during a prolonged period of time can be desirable. In *Chapter 6* the safety and efficacy of a practical, bodyweight-dependent algorithm to establish euglycaemia in patients with diabetes is assessed. Moreover, there is an increasing need for an accurate, swift and easy to operate method of glucose determination. In *Chapter 7* a portable glucose analyser that can be used pre-analytically and bedside, HemoCue, is assessed for accuracy in comparison to a glucose oxidase method which is frequently used as standard method, in particular for hypoglycaemic values. To explore the practical implications of the research described in this thesis, for patients with diabetes and for society, in *Chapter 8* laws and regulations in the Netherlands concerning diabetes are studied. Finally, all results are summarised and interpreted in *Chapter 9*. Moreover, in this chapter recommendations based on the studies described in this thesis are made.

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Chapter 2 Diabetes and driving: desired data, research methods and their pitfalls, current knowledge and future research

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Introductory paragraph

The issue of traffic safety of patients with diabetes mellitus is rising on political as well as scientific levels. Driving by diabetic patients may be impaired by three factors: hyperglycemia, hypoglycemia and diabetic complications. Management of diabetic patients is progressively aiming at near-normoglycemia[1,2]. Consequently, the rate of hypoglycemia and hypoglycemia unawareness has markedly increased[3-8]. These factors could pose an increased threat to diabetic patients' fitness to drive. Current legal restrictions regarding diabetes and driving privileges vary throughout the world, but laws are generally prompted by the impending danger of hypoglycemia during driving. To research the various aspects of diabetes and driving, several study methods have been applied. In consideration of dissenting opinions and laws, rules and regulations, in this article we will discuss the currently available data on diabetes and driving, potential pitfalls in research and give recommendations for future research.

Introduction

In modern traffic, the increasing age of drivers[9] and their medical conditions, can be risk factors for traffic incidents and accidents. The amounting prevalence of diabetes also leads to an increased number of diabetic drivers. Driving by diabetic patients may be impaired by three factors: hyperglycemia, hypoglycemia and diabetic complications. In recent years it has become apparent that acute hyperglycemia, and possibly also chronic hyperglycemia, may be associated with cognitive function loss[10-15]. However, the cognitive dysfunction occurring during hypoglycemia is most striking[16-18]. After the DCCT[2] and the UKPDS[3], which showed that diabetic complications are reduced with tight glucose control, management of diabetic patients is progressively aiming at near-normoglycemia. Consequently, the rate of hypoglycemia has increased. We now know that even a single episode of hypoglycemia leads to impaired hypoglycemia awareness[19]. Hypoglycemia unawareness currently affects approximately 25% of patients with type 1 diabetes[4-6]. The incidence of severe hypoglycemia in type 2 diabetes is lower[3,6,7]. but may approach the incidence in type 1 diabetes[3,8]. Sequellae of diabetic complications (e.g. retinopathy, neuropathy)[20-22] can impair driving capacity; retinopathy is associated with impaired vision,, and its treatment with laser coagulation may reduce peripheral vision[23-25]. Peripheral neuropathy may interfere with the operation of a vehicle. Eventually the challenge will be to identify individual diabetic drivers who have an impaired fitness to drive.

Legal regulations

Laws, rules and regulations regarding medical conditions have to balance individual interests on one side against the general interest of traffic safety on the other side, and therefore the safety risks of granting driving privileges to a certain group of people with a (possibly) increased risk of automotive accidents have to be estimated. Social and economic factors play an important role: young males have higher accident

rates[26-28], as do drivers from lower social classes[29-32], and drivers of advanced age are more likely to have fatal accidents[26,33-36]. Nevertheless, these groups are not excluded from driving. Likewise, weather conditions, such as night driving or rain may entail higher risks than the diabetic condition[37,38]. Current legal restrictions are generally prompted by the impending danger of hypoglycemia during driving. The possible interference of chronic diabetic complications is also taken into account.

In Europe, many countries have restrictions for diabetic drivers, ranging from more frequent than usual medical examination to denial of driving privileges for certain groups, e.g. patients with hypoglycemia unawareness. The European Union has issued directive 91/439, stating that diabetic patients who are using insulin are excluded from driving trucks, heavy goods vehicles and buses, except for small trucks in "very exceptional cases"[39]. This directive is interpreted differently throughout the EU[40,41].

Many US states have a restrictive licensing program for drivers with medical conditions[42,43]. Utah, for example, has a program that may impose restrictions on speed, geographic area, or time of day. In California, it is mandatory for doctors to report unexpected loss of consciousness due to hypoglycemia to the authorities, which results in revocation of the driving license. In most states such reporting is voluntary or permissive. Individuals with diabetes who are treated with insulin are automatically denied an interstate commercial driving license, with exception to some states[42-44]. However, during the past decennium in 39 out of 50 states waivers were temporarily granted[44].

Current knowledge

Office-based surveys and questionnaires

Several studies have been published with office-based samples of diabetic patients. In 1980 Clarke et al. found that 40% of 94 insulin-dependent drivers admitted having experienced hypoglycemic symptoms while driving[45]. In the same year, Frier et al. reported that 13.6% of 250 patients with insulin dependent diabetes had been involved in a driving accident since starting insulin treatment, and 5.2% suspected that hypoglycemia had been a causal factor[46]. Steel et al. reported that only five of 120 type 2 diabetic patients patients had experienced mild hypoglycemia while driving, and none admitted to a driving accident related to hypoglycemia[47]. Eight years after the original survey of Eadington and Frier, 20% of their 250 patients admitted to have experienced hypoglycemia while driving. Interestingly, the mileage-adjusted accident rate for the whole group was 5.4 per million miles driven (men 4.9; women 6.3), which was considerably lower than the accident rate for the general population of 10.0 accidents per million miles[48]. Stevens et al. found, among 354 insulin treated diabetic drivers in Belfast, a similar accident rate of 7.9 per million miles, which was 7.8 in a control group. Since these rates were only calculated for the 24% of cases and controls who reported accidents, true accident rates must have been lower[49].

Songer et al. reported a trend towards a higher accident rate in 121 insulin dependent diabetic patients versus 121 case-controls in Pittsburgh, Pennsylvania (10.4 vs. 3.9 accidents per 100 drivers per million miles; P=0.12), especially in women. There were no data on type of road, type of vehicle, time of day, severity of accidents, etcetera, which all may have been confounding factors[50]. In a large multi-centre, multinational survey in seven US and four European cities with 313 type 1 and 274 type 2 diabetic drivers, 159 of whom were using insulin, type 1 diabetic drivers reported more crashes and moving violations than type 2 diabetic drivers or non-diabetic spouses (19% vs. 12% and 8%, respectively, P<0.001)[51]. However, results were given as percentages of individuals with accidents or mishaps, and were not corrected for number of accidents or mileage, since some drivers with diabetes and multiple motor vehicle accidents had substantially reduced their driving. Perhaps the most worrying figures concerned the occurrence of hypoglycemia during driving. Of the type 1 diabetic drivers in the US 31%(!) admitted to have driven in a hypoglycemic stupor during the past two years, and 28% experienced hypoglycemia while driving in the past six months. These figures were considerably lower for the type 2 diabetic drivers (8% and 6%, respectively). In diabetic drivers from Europe, occurrence was strikingly lower: 4% and 16% for type 1, respectively. No hypoglycemic episodes behind the wheel were reported by European type 2 diabetic drivers[51]. In most of these studies essential data on patient, treatment and mileage is missing, and control groups, if present, were not always well matched. None of the studies provides information on the circumstances or severity of the crash.

Hospital registry based research

In a study in Western Australia, from 1971 to 1979 in 8623 diabetes patients, overall admission rates of diabetic drivers were not higher than non-diabetic drivers, but,

there was a significant excess of admissions in diabetic men under 55 years of age, both as drivers and as pedestrians[52]. Hansotia and Broste, studying hospital records of 484 diabetes patients (436 type 2 diabetes, 69.5% using insulin) from Marshfield, Wisconsin, found a slightly elevated accident ratio (1.32; P=0.01). Unfortunately the accident ratio was not corrected for miles driven. For traffic violations this ratio was not significantly elevated (1.14; P=0.23)[53]. In a Dutch case-control study, prevalence of diabetes was slightly lower among drivers admitted to the emergency room (1.2%), than in the general population (1.3%). The finding that prevalence of diabetes was higher in passengers casts doubt on the validity of the data[54]. Most recently, in a study of 11,244 patients in the Scottish Trauma Audit Group database who were admitted to the hospital for 3 or more days, or died in the hospital as a result of an accident, only 23 patients with insulin-treated diabetes were identified. The road traffic accident rate for insulin-treated patients was estimated at 44.4 per 100.000 persons per year, compared with 34.4 for the general population (relative risk 1.29; P=NS)[55].

In addition to the possible methodological problems with studies based on hospital records that will be discussed below, in all of the studies mentioned, information on the driving habits of the patients and particularly on crash variables is very limited or absent, reducing comparability and validity. However, the slightly increased accident rate per number of drivers is a consistent finding in most of these studies[52,53,55].

Research based on records of authorities

A number of studies originate from 1970 or earlier[56-59], when traffic was very different from current times, and treatment of diabetes differed from current practice. They report inconsistent higher, lower and equal accident rates among diabetic patients as compared to controls.

More recent studies include an Icelandic study, in which all drivers in single-car accidents between 1989 and 1991 (n=471) were sent a questionnaire about driving habits, drinking habits and chronic disorders, including diabetes mellitus. Single-car accidents could represent accidents solely due to driver-related factors, such as alcohol and drug use, and medical disorders. Incidence of diabetes mellitus was very low, and similar in the study group and a control group of 999 people chosen at random from the general population (both 0.6%)[60]. McGwin et al. studied 447 randomly selected drivers who were 65 years or older, and had been involved in one ore more road traffic accidents during 1996 in Alabama by means of telephone interviews. After adjustment for age, sex, race and annual mileage, the odds ratio for diabetes was 1.1 (95% confidence interval 0.7-1.9) when compared to both a control group and a group drivers not-at-fault. Strikingly, among subjects who had been at-fault for an accident in the 4 years preceding, the adjusted odds ratio for diabetes was 2.5 (0.9-7.2), while it was only 0.9 (0.5-1.7) among those who had not had an accident in the previous 4 years. This suggests that there is a subgroup of (older) drivers with diabetes that could be at increased risk for road traffic accidents[61]. Most recently, the National Highway Traffic Safety Administration (NHTSA) linked police crash records of 68,770 drivers to medical and financial information. In drivers known for diabetes (and other metabolic conditions!; number not given) with an unrestricted driving license, the relative risk for at-fault accidents was 1.44 (P≤0.05). In drivers with restricted driving

licenses because of metabolic conditions the relative risk was 3.56 (P=NS)[62].
Taken together, although various studies find an increased accident rate among diabetic subjects, other studies do not, or even show a lower rate. Some studies had relatively small numbers of diabetic patients. The methodologically most accurate study by McGwin et al.[61] on drivers over 65 years of age indicates that there might be specific subgroups of diabetes patients that are at increased risk.

Insurance record based research

Koepsell et al. reviewed the records of a group health insurance in Washington State, identifying drivers over 65 years who were injured in a road traffic incident during a two year period, comparing them to 446 case-controls not involved in an accident[63]. A total of 234 cases were identified, of which only 26 were known for diabetes. The authors found a 2.6-fold increased injury-risk in older diabetic drivers. In the six(!) insulin treated patients, the odds ratio was 5.8, 95% confidence interval 1.2-28.7. The odds ratio for twelve patients using oral hypoglycemic agents was 3.1, not statistically significant, and for diet alone 0.9. Interestingly, patients with both diabetes and coronary heart disease had an odds ratio of 8. It must be noted that the number of diabetic patients was extremely low. Clearly, the number of diabetics was low, although the study may indicate a trend[63]. The Danish Diabetes Association, offering all members a free collective accident insurance, reported that the risk of any accident was significantly lower in the diabetic group as compared to two control groups (0.7 per 1000 person-years, versus 4.5 and 5.5, respectively). Only one car accident was reported[64].

Driving simulator studies

Two driving simulator studies, in which hypoglycemia was induced by means of a hyperinsulinemic clamp, have been performed by the group of Cox et al.[65,66]. In a group of 25 type 1 diabetic patients, driving four minutes in a low-fidelity driving simulator, they found driving performance not disrupted at mild hypoglycemia (3.6 mmol/l). During moderate hypoglycemia (2.6 mmol/l) driving performance was reduced, with significantly more swerving, spinning, time over the midline, and time off the road. In addition, there was more compensatory very slow driving. Strikingly, only 50% of the subjects with reduced driving performance stated that they would not drive under similar conditions in everyday life[65]. In a second simulator study, 37 type 1 diabetic patients drove 30 minutes during progressive hypoglycemia, from 4.0 mmol/l to below 2.8 mmol/l. When subjects felt hypoglycemic, they were given the opportunity to self-treat the hypoglycemia by drinking a (placebo) glucose drink or to discontinue driving. Diminished driving performance was observed at all glucose levels (4.0-3.3, 3.3-2.8 and <2.8 mmol/l), although this was only seen for a limited number of parameters, with no consistent pattern. During hypoglycemia eleven subjects treated themselves, and seven subjects stopped driving. Thus, only 32% of patients took corrective action, whereas 79% detected hypoglycemia below 2.8 mmol/l. This indicates that, even in an experimental setting, only a relatively small percentage of diabetic patients take appropriate action on experiencing hypoglycemia during driving[66]. However, the use of a low-fidelity, fixed-base, non-mock-up (no

model of a real car around the simulator) driving simulator is probably not appropriate to assess complex aspects of driving[67]. Furthermore, in such a complex study (awareness of impending hypoglycemia; intravenous lines; EEG-cap; questions posed during driving) a control group is essential for validity.

Blood Glucose Awareness Training

Cox et al. have also developed Blood Glucose Awareness Training (BGAT), a patient education program, designed to teach patients to more accurately estimate blood glucose levels[68-70]. Remarkably, after four years follow-up, accident rates per million miles driven were 6.8 in the BGAT group versus 29.8 in the diabetic control group (P=0.01), presumably due to an increased awareness of when not to drive[70]. During long-term follow-up the number of traffic violations was significantly reduced from baseline. However, there was no clinically relevant improvement in patients' avoidance of driving with low blood glucose levels (48% to 51%). The rate of road traffic accidents was not mentioned. Similarly, in a Dutch study on BGAT, the decision not to drive during hypoglycemia improved significantly (P=0.01) and patients were less often involved in a traffic accident (0.6 vs. 0.2 accidents/patient/year; P=0.04)[71,72]. BGAT may well be a relatively easy and effective method to reduce traffic violations and accidents in diabetic patients.

Commercial truck driving

Since chances of injury, the number of injuries and the severity of injuries are higher in trucks[73,74], stern restrictions have been imposed on driving privileges for vocational drivers with diabetes[39-41,44]. Based on various assumptions, Lave and Songer have estimated that, if diabetic patients would be licensed to drive commercial motor vehicles, mild and moderate hypoglycemia would increase the amount of accidents 6.1-fold for insulin-dependent diabetic patients and 4.1-fold for non-insulin-dependent diabetic patients, resulting in an additional 42 accidents per year in the United States. The risks of diabetic drivers with a history of severe hypoglycemia would be increased nearly 20-fold. However, they also estimate that if these latter diabetics are excluded, the relative risk drops to 3.7 and 2.7, respectively, and the number of additional accidents per year to 20[75]. In a companion paper the same authors conclude that, given the fact that other higher risks, are generally accepted (e.g. driving licenses from the age of 16, allowing some unsafe motorways, etcetera), the additional risks from insulin using persons are well within the accepted range of risk[76]. A Canadian research group merged a number of databases of the Quebec Automobile Insurance Society, providing information on driving licenses, accidents, traffic violations, and medical conditions of over 20,000 license holders, 1,198 of whom were commercial motor vehicle drivers who responded to a telephone survey[77]. The number of diabetic drivers remains unclear. Strikingly, in each of six different regression models diabetic drivers in straight trucks had a significantly higher number of road traffic accidents. Since this was not found in articulated trucks, it could be that the physically and medically fittest drivers were selected for the largest (articulated) trucks[77]. In an extension of this study, Laberge-Nadeau et al. analyzed the severity of road traffic accidents of commercial motor vehicle drivers, and found no significant association between diabetes and crash severity was

found for either type of truck[78]. In 2000 the group again reports, on what appears to be the same cohort during the same period, that only drivers with a license for single (unarticulated) trucks, not using insulin and without diabetic complications, had an increased relative risk of 1.76 (95% confidence interval 1.06-2.91). All other subgroups of diabetic truck drivers, had relative risks of approximately 1 (0.65-1.02), and therefore insulin use was not associated with higher crash risk. The previously suggested "healthy workers effect" is supported by the fact that the percentage of drivers holding the license that is actually driving commercially is similar in the control group and in the group of diabetic drivers in good health. This percentage is considerably lower in the group of diabetic drivers with complications or using insulin[79].

Although the suggested explanation is plausible, other, more methodological, problems remain. First, about one third of the known drivers were not included in the studies, for various reasons. Second, a number of variables, including mileage, working hours and number of hours behind the wheel were obtained through a telephone survey. It could be that, because of their medically restricted driving licenses, diabetic drivers were more reluctant to admit to driving more miles or longer hours, thus influencing results. However, the studies clearly indicate that an increased risk for (a subset of) diabetic truck drivers could very well exist.

Older diabetic drivers

It has been well established that older age is associated with poorer driving performance[80], a higher number of road traffic accidents per mile driven and a higher likelihood of injury or death[33-36]. Moreover, cognitive functioning seems to decline more rapidly in older diabetic patients than in healthy subjects[81,82]. The two largest studies on diabetes and driving in the elderly have been discussed above[61,63]. Koepsell found a 2.6 fold increase in injury risk for diabetic drivers, which was even higher (odds ratio 5.8) for patients treated with insulin or oral hypoglycemic agents (odds ratio 3.1), and for drivers with a duration of diabetes over 5 years (odds ratio 3.9)[63]. McGwin only found an association with accident involvement among diabetic subjects already involved in a road traffic accident in the previous 4 years, but found no increased risk for the whole group of elderly diabetic drivers, nor for treatment modality[61]. Forrest et al. reported a clear and significant association between diabetes and driving cessation in 1768 women of 71 years and older (odds ratio 2.53, 95% confidence interval 1.57-4.07). This implies that older diabetic drivers are more likely to give up driving than those who do not have diabetes[83]. One may argue that older diabetic drivers adequately self-regulate their driving pattern. These results are confirmed by Gallo et al., who found that in 589 subjects aged 60 years and older, driving cessation was (slightly) more likely in drivers with diabetes (odds ratio 1.37, 95% confidence interval 1.03-1.83). In this group, there was no association between diabetes and road traffic accidents or violations (odds ratio 0.88, 95% confidence interval 0.50-1.53)[84].

Accident frequency due to medical conditions

In British and American research it was shown that roughly 95% of road traffic accidents are attributable to human errors, or defects from the vehicle, the road or the

environment[85,86]. Various European studies indicate that only 0.4 to 3% of lethal accidents were caused by medical conditions[87-89]. Epilepsy appears to be the commonest cause (38%), with insulin treated diabetes to be the cause in 18%, acute myocardial infarction and stroke each in 8%. No cause could be established in 21%[86].
Harsch et al. found in 450 randomly selected German patients with both type 1 and type 2 diabetes that symptomatic hypoglycemia during driving was rare, with an occurrence of 0.19-8.26 per 100,000 kilometers driven, or 0.02-0.63 per year driven. The incidence increased significantly with the "strictness" of treatment, with odds approximately fourfold higher during intensified insulin treatment and CSII than during oral treatment. Traffic accidents due to hypoglycemia occurred 0.01-0.49 times per 100,000 kilometers driven or 0.007-0.01 per year driven. Strikingly, there was no difference in accident-rate between treatment modalities[90]. Given the fact that the diagnosis of hypoglycemia can be quite difficult, it may well be that episodes of hypoglycemia causing a road traffic accident have remained unrecognized or have been wrongfully diagnosed[91]. Nevertheless, it can be concluded that only a very small proportion of road traffic accidents are caused by a medical condition in general and by diabetes in particular.

Desired data, research methods and pitfalls

Desired data

To objectively and accurately consider the relationship between diabetes and driving, ideally, valid data should be available on the following aspects of driving in patients with diabetes: accident rate; driving performance; the effect of diabetes-related factors; and the possibility of modification of certain aspects.

Ultimately, whether patients with diabetes cause more accidents seems paramount. However, the mere accident rate does not provide sufficient information. Nature and severity of accidents are important parameters. Data should be corrected for relevant variables, including age, gender, driving experience, miles driven per year and road type. In patients with diabetes there may also be other confounding factors including type of diabetes, treatment modality, and hypoglycemia awareness. Patients may impose restrictions to themselves, e.g. on driving frequency, distance or on conditions (night time, bad weather, etc.). Moreover, the relation between accidents on the one hand, and diabetes proper and glycemic status during the accident on the other hand, should be assessed. Furthermore, certain (subclinical) diabetic complications could negatively influence driving performance and could increase the accident risk. This is evident for retinopathy, cataract and neuropathy, but in recent years it has also become known that in patients with diabetes the brain may suffer changes similar to the effect of ageing[81,82]. Therefore, data on driving performance as such are equally important. Patients with diabetes are by no means a homogenous group. Treatment, incidence of hypoglycemia, diabetic complications, and hypoglycemia awareness can vary considerably between groups, but also between individuals. For these reasons, it is important to identify subgroups of patients who are at increased risk. Finally, after identification of the factors that negatively influence driving performance and accident risk in patients with diabetes, the next step will be to investigate whether and how these factors can be positively modified.

Research methods and pitfalls

To research the various aspects of diabetes and driving, several study methods have been applied, each of which entails potential strengths and biases. Most frequently, accident rates have been analyzed in various samples of diabetic patients.

Office based research In office-based samples (usually out-patients from a general or diabetes clinic) the possibility of selection-biases exists. These may be related to the type of clinic, the selection of patients by physicians and willingness and opportunity of patients to participate. Finally, there could be a "survivor bias" (patients having had a lethal accident cannot participate in the study).

Hospital and authority record based research Some studies have focused on samples of subjects who had recently experienced road traffic accidents[52-62]. These subjects may have been identified in hospital and emergency room records[52-55], or records of police and other authorities[56-62]. Records of emergency room and hospital admission could also carry a "survivor-bias" or the opposite, where patients in a certain group could have more light road traffic accidents, not requiring transportation to an emergency

room. Moreover, in countries where health personnel is obligated to report disease-related traffic accidents (e.g. California), patients who have had a collision because of hypoglycemia will be reluctant to be transported to a hospital. Police records could be more representative, although in countries where police presence after an accident is not mandatory, biases could occur. Only three studies have been performed involving insurance-records[63,64,77-79], which are most likely to be representative and complete. Perhaps for commercial reasons, insurance companies have been reluctant to co-operate in scientific research. In all studies with authority based records, there is a potential bias in reporting of the incidence of diabetes to the authority by the patient, as this is not mandatory in many countries. Patients who are most likely to experience problems with driving, are most likely to not report their diabetes to the insurance company or licensing authority.

Questionnaires In many (retrospective) studies, information is obtained through questionnaires, filled out by the drivers themselves[45-51,70,72,83,84]. This can cause a recall-bias on the one hand and a bias of subjectivity on the other hand. Often, subjects filling out questionnaires tend to neglect negative experiences, or describe occurrences in a more positive fashion[92]. The value of questionnaires is therefore limited.

Driving simulator research Driving simulation studies have potential advantages over other types of studies since they examine driving performance specifically; circumstances as urban driving, highways, but also weather conditions can be simulated in a standardized manner. This research method relies on comparative measurements. Thus, it cannot be claimed that simulator results have absolute validity, but only that differences found between conditions or groups represent differences that exist in reality. Therefore, it is an indirect measure of the relative risk of road traffic accidents. However, good correlation has been shown[67,93]. When employing driving simulation as a research tool, it is of importance to utilize a suitable driving simulator and appropriate programming. A high-fidelity driving simulator, where reality is closely approximated, is required to assess more complex aspects of driving, like driving performance. A low-fidelity simulator can be used be used to research other hypotheses, for example concerning behavior and decision making of patients with diabetes[67].

Conclusions and recommendations for future research

Conclusions

When performing research on the relationship between diabetes and driving, several study designs can be applied, each of which entails potential strengths and biases. Evaluation of the available research on diabetes and driving is difficult. Most older studies have either found no association between diabetes and traffic accidents, or a small, usually not statistically significant, increase of the relative risk. More recent US research however, indicated a clear trend, frequently statistically significant, towards a slightly increased risk of road traffic accidents in diabetic drivers. The increase of the relative risk in some studies was only found in specific subgroups of diabetic patients, not consistent throughout various studies. Overall the available studies indicate that road traffic accidents directly caused by diabetes seem to be relatively rare occurrences. However, without a doubt hypoglycemia during driving does occur, and can cause traffic accidents. If any trend can be distilled, current knowledge may point towards a slightly increased risk of road traffic accidents for drivers with diabetes mellitus. However, no subgroup that is particularly at risk has been unequivocally defined.
The appraisal of potential risks of participation in traffic of a certain group of people, versus the social aspects of denying participation, may be influenced by society, media and experts, but final appraisal should be performed by the legislators.

Recommendations for future research

At this point in time, to increase current understanding, support decisions on legislation concerning diabetes and driving, and to tailor legislation to specific subgroups at risk, three types of research would be most helpful:
First, a large, multi-centre, multinational, prospective follow-up study on the rates of traffic accidents and incidents of patients with diabetes in comparison to a well matched control group from the general population. The study should be performed in countries or states where reporting of diabetes to a central authority is mandatory, and where all traffic accidents and violations are registered by either police or insurance companies, including all relevant information. Also, relevant diabetes-related information should be available, to identify specific subgroups at risk for road traffic incidents or accidents, with a specific focus on older drivers. Information of particular relevance may include therapy (hypoglycemic drugs, insulin, insulin pump), duration of diabetes, diabetic complications, and self monitoring of blood glucose, specifically before and during driving. On the other hand information on age and socio-economic factors should be available, including school education, income, alcohol use, and drug abuse. It might well be that the latter socio-economic factors may prove to be more relevant for traffic accidents and violations than diabetes per se. When possible, data on commercial vehicle drivers should be collected as well.
Second, regarding glucose awareness, programs such as BGAT, are potentially very useful, and their implementation in clinical practice should be considered. Future research should focus on their long-term efficacy, and the necessity of repetitive

glucose awareness instruction; in addition, its use in specific subgroups such as patients with neuropathy, hypoglycemia unawareness, or (future) insulin pump users, may be studied.
Third, research on driving performance of various groups and subgroups of patients with diabetes should be performed, preferably in a well validated state-of-the-art driving simulator. It should primarily focus on driving performance and on the influence of hypoglycemia and hyperglycemia. Subsequently, specific subgroups of patients with diabetes with impaired driving performance should be identified. If future research would indicate that hyperglycemia itself is associated with decreased driving performance, screening for (unknown) diabetes might be considered, for example in specific groups such as commercial drivers, or drivers over a certain age. Other driving simulator studies may investigate the impact of BGAT on driving performance. Finally, when subgroups of patients who are at increased risk of road traffic incidents and accidents have been identified, research should subsequently focus on altering factors that influence the increased risk, including behavioral, pharmacological and technical possibilities.

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Chapter 3 Driving performance and effort needed to drive of patients with type 1 diabetes mellitus during euglycemia and moderate hypoglycemia in a state-of-the-art moving- base driving simulator

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Abstract

Background

The influence of diabetes mellitus on driving behavior and the occurrence of traffic incidents remains controversial. Several studies have addressed accident rates in patients with diabetes. Results vary considerably and their validity is limited. We aimed to assess driving performance in patients with type 1 diabetes during euglycemia and moderate hypoglycemia.

Methods

We studied 45 type 1 diabetic subjects, 24 with normal hypoglycemia awareness, and 21 with impaired hypoglycemia awareness, and 24 healthy controls, in a state-of-the-art moving-base driving simulator. Driving was studied in different environments (highway, rural road, and built-up areas) during clamped euglycemia (5.0 mmol/l) and moderate hypoglycemia (2.7 mmol/l). In addition to uneventful driving, some unexpected events were programmed to occur. Also, a continuous peripheral detection task was applied to monitor drivers' workload. Various driving parameters were measured.

Results

No significant differences in driving performance were detected during euglycemia in either group of type 1 diabetic subjects, as compared to the healthy controls. The effort needed to drive was slightly higher in both study groups when driving in critical situations in built-up areas. During moderate hypoglycemia, which was accompanied by marked hypoglycemic symptoms in the normal hypoglycemia awareness group, neither driving performance nor workload deteriorated significantly for either patient group.

Conclusions

Patients with type 1 diabetes showed good driving performance during both euglycemia and moderate hypoglycemia (2.7 mmol/l). These results suggest that moderate hypoglycemia does not influence driving performance in type 1 diabetic subjects, thus allowing patients with normal hypoglycemia awareness to take appropriate measures when moderate hypoglycemia occurs during driving.

Introduction

Driving privileges for patients with diabetes mellitus are currently under discussion. Throughout the world, restrictive legislature concerning insulin-using diabetic drivers has been issued. In recent years, restrictions for issuing driver's licenses in Europe have been increased[1], whilst in the United States of America authorities are working towards more liberal policies[2]. However, the influence of diabetes on driving behavior and the occurrence of traffic incidents remains controversial. Accident rates in cohorts of diabetic patients have been examined in several studies. Some studies show higher accident rates in patients with diabetes[3-7], while other studies show lower accident rates[8-9]. In most studies no differences are reported[10-14]. Validity of these data is questionable, as all of these studies are retrospective, and most have major methodological drawbacks[15,16]. Current legislation was prompted largely by the possibility of hypoglycemia occurring during driving. This concern has become more imperative, as rates of hypoglycemia in patients with diabetes are rising, now that management is progressively aiming at near-normoglycemia[17,18]. In addition, prevalence of hypoglycemia unawareness has increased, currently affecting approximately 20-30% of people with type 1 diabetes[19,20]. Although it is well known that hypoglycemia impairs cognitive performance in standardized tests[21-23], the practical effects of moderate hypoglycemia on driving performance, and the role of hypoglycemia unawareness, have not been well established.

A driving simulator is commonly used in traffic psychology as a tool to assess situations that do not yet exist in reality, that are potentially too risky to evaluate in reality, or that cannot be replicated at will (so that the required level of control may not be reached). It provides the opportunity to apply a standardized test, in which different aspects of driving performance can be measured objectively. Thus, driving simulators have already been used to assess differences in performance between subjects with ailments and controls[24-27]. We studied driving performance in patients with type 1 diabetes, with both normal and reduced hypoglycemia awareness, and the effect of moderate hypoglycemia on driving performance, using a state-of-the-art driving simulator.

Methods

Subjects

Patients were recruited from the outpatient clinic of the University Medical Center Utrecht, Utrecht, the Netherlands. Eligibility criteria included age between 20 and 65 years, at least two years of type 1 diabetes mellitus, C-peptide negativity, absence of cardiovascular disease or neuropathy, visual acuity >16/20 in both eyes, possession of a driving license for at least two years, and at least 5000 miles driven in the past year. Healthy control subjects were recruited at random from the general population. They had to meet the same eligibility criteria, but could not have diabetes or any other disease potentially interfering with driving performance. No subject could use medication influencing hypoglycemia counter regulation or the ability to drive, or have any experience with the driving simulator. The study was approved by the institutional review board of the University Medical Center Utrecht, and all subjects gave written informed consent.

Driving simulator

To objectively assess driving performance, the Netherlands Organization for Applied Scientific Research (TNO) state-of-the-art driving simulator in Soesterberg, the Netherlands, was used. The driving simulator consisted of several subsystems:

a) A mock-up of a Volvo 240 sedan (automatic gearshift), with all normal instruments at the driver's disposal. Steering wheel and accelerator and braking pedals were equipped with a force-feedback system.
b) The vehicle model computer calculated the position of the vehicle, velocity, and heading, based on the input ("driving") of the subject.
c) The supervisor computer coordinated communication between subsystems, data storage, and behavior of other simulated traffic.
d) A computer generated image system, based on data input from the vehicle model. Images were projected onto a screen (radius 3.75 meters) in front of the mock-up by three high-resolution projectors.
e) The mock-up was equipped with a nearside and offside wing-mirror as well as a rear-view mirror.
f) Sound of the vehicle (engine, wind, tires) and other vehicles was generated with a sampled sound system sampler.
g) The mock-up was situated on a moving base with six degrees freedom in all directions, to realistically simulate road contact, acceleration, deceleration, et cetera.

Interaction with other traffic took place at all times.

In addition to driving performance per se, the mental effort needed to obtain a certain level of performance was assessed by having subjects continuously perform the Peripheral Detection Task (PDT), a generally accepted method for estimating workload. A red light stimulus (dot) was presented for one second at a horizontal angle of between 11° and 23° with a random inter-stimulus interval of 3 to 5 seconds. The driver had to respond to the stimulus by pressing a response button attached to the dominant index finger. The reaction time, as well as the percentage of missed signals, increase

with higher driver workload or effort, and thus reflect the effort drivers need to execute the primary driving task[28-31].

Speed, right lane crossing, left lane crossing, PDT reaction time, and missed PDT-signals were measured by the vehicle computer during straight driving (all road types), and during critical situations. Critical situations were: approaching a traffic jam, braking vehicle in front, and package falling of truck (motorway); approaching crossing, overtaking of slow vehicle in front, and wide curve (radius >2000 m) (rural road); narrow curve (radius <500 m), medium curve (radius 500-2000 m), wide curve, pedestrian crossing road, car crossing road, and approaching stop sign (built-up areas). This simulator was previously described[32], and has been validated extensively[33-36].

Procedure

Patients were withdrawn from long and intermediate acting insulin for 24 hours before the study and managed with short-acting insulin. Patients using oral glucose lowering agents were withdrawn from these agents 24 hours prior to the study. Subjects arrived at 8:00 PM on the evening before the study. Two antecubital veins were cannulated. No caffeinated beverages were consumed. Subjects were given a bedtime snack at 11:00 PM, and remained fasting until the end of the study. In patients, nocturnal near-normoglycemia was maintained, using a variable, low-dose insulin infusion37. In the morning, all participants drove a thirty-minute test run to get accustomed to the simulator and minimize learning effects. Subsequently, a hyperinsulinemic glucose clamp was started with insulin (Human Actrapid, Novo Nordisk, Gentofte, Denmark) infused at 2.0 mU/kg/min, and dextrose 20% administered at a variable rate. Arterialized venous blood samples (55 °C) were obtained every 5 minutes, and plasma glucose was measured (YSI 2300 STAT, Yellow Springs Instruments, Yellow Springs, OH, USA). Subjects were blinded for their plasma glucose level.

Subjects completed two sessions of three runs in the driving simulator. Runs lasted minimum 8 minutes, and were staged on a highway, on a rural road, and in built-up areas. There were two scenarios per road type, assigned in a randomized, cross-over fashion. Before and after each run, plasma glucose concentration was checked during a one minute interval, to ensure that the target plasma glucose level was maintained. The first driving session was driven with a plasma glucose concentration of 5.0 mmol/l. Subsequently plasma glucose was lowered to 2.7 mmol/l in patients, whereas in control subjects 5.0 mmol/l was maintained. After 60 minutes, the second driving session was performed. Each subject drove a total of at least 48 minutes. Cannulas and intravenous lines did not interfere with any movement required for driving. At baseline and immediately before and after each driving session, blood was drawn to measure epinephrine levels (HPLC-essay, Chromesystems, Munich, Germany). Also, before and after each driving session, subjects rated each of the following hypoglycemic symptoms from 0 (none) to 6 (severe) in a semi-quantitative questionnaire: palpitations, anxiety, tremor, sweating, cold hands, numb lips, dry mouth (autonomic symptoms); difficulty concentrating, blurred vision, impaired speech, confusion (neuroglycopenic symptoms); difficulty breathing, painful legs,

seeing yellow halos (dummy symptoms).

Statistical analysis

The experiment was powered to detect minute differences in driving performance. For 80% power at z=0.2, a group size of 18 would be required. Test-retest correlation was assumed to be 0.95[38,39].
Before data analysis, it was established for each patient whether there was a significant rise in epinephrine levels or symptom scores during hypoglycemia as compared to euglycaemia, defined as exceeding the 95% confidence limit observed during euglycemia, as previously described[40]. Patients were identified as having normal awareness for hypoglycemia, if there was a significant rise in both parameters.
Analysis of variance (ANOVA) was applied to test for main effects of study group versus controls, as well as for the hypoglycemic versus euglycemic conditions, corrected for learning or fatigue effects during the second run (Group*Trial interaction). α (one-sided) was 0.05.

To allow interpretation of the large amount of data, it is common practice to create composite parameters of driving performance and PDT,[29,30,33-36,41-47]. For this purpose, the magnitude of effect was estimated for all effects that were significant at the 0.05 level. Standardized difference scores (z-scores) were calculated, defined as the difference between the average scores of two groups, divided by their common standard deviation[48]. If the effect was not significant, the z-score was 0. Thus, for each separate parameter, a z-score for straight (uneventful) driving was obtained, and various z-scores for critical situations. The average z-score of all critical situations was calculated. Subsequently z-scores of driving parameters and PDT parameters were averaged. For driving, even weight was given to average speed, right lane crossing and left lane crossing. For workload even weight was given to PDT reaction time and missed PDT signals. As a result, composite z-scores were achieved for driving performance and PDT during uneventful driving and critical situations. Commonly used labels for standardized effect sizes that may assist in their interpretation are 'small' (z = 0.20-0.50), 'moderate' (z = 0.50-0.80) and 'large' (z >0.80)[48]. Post-hoc analyses were performed using Fisher's exact test. Other data will be presented as mean (SD), with a two-sided 5% level of significance in Student's t-tests.

Results

A total of 45 patients with type 1 diabetes mellitus were enrolled in the study. Twenty-four of these patients were identified as having normal hypoglycemia awareness (NHA), 21 patients had impaired hypoglycemia awareness (IHA). Twenty-four healthy control subjects were matched for age, gender and driving experience. Mean age was 35.3 ± 8.0, 40.4 ± 10.8 and 39.4 ± 11.9 years, respectively. BMI was 26.5 ± 4.0, 24.9 ± 2.9 and 24.5 kg/m², respectively. Driver's licenses were held 15.0 ± 8.7, 20.3 ± 10.3 and 18.8 ±10.8 years, with currently 25458 ± 28945, 21450 ± 14849 and 24917 ± 23405 kilometers driven per year, respectively. There were no statistically significant differences. Duration of diabetes was 14.8 ± 8.0 years in the NHA group and 19.5 ± 10.0 years in the IHA group (P=.09). HbA_{1C} was 8.2 ± 1.0 and 7.8 ± 1.1% (P=.24), respectively.

Glucose clamp

During the first driving session plasma glucose concentrations were maintained at 5.06 ± 0.77 mmol/l in all groups (P=.97). During the second driving session plasma glucose concentrations were lowered to 2.74 ± 0.36 mmol/l in both patient groups (P=.46) and maintained at 5.08 ± 0.76 mmol/l in the control group (P<.0001 to patients groups) (FIGURE 1A).

Epinephrine concentrations and symptom scores

To demonstrate that during the second (hypoglycemic) driving session, patients had symptomatic hypoglycemia for the NHA group, and no biochemical counter regulation or hypoglycemic symptoms for the IHA group, epinephrine concentrations and symptom scores were assessed before and after each driving session.

Figure 1a-c. Plasma glucose concentrations, plasma epinephrine concentrations and total symptom scores during the study.

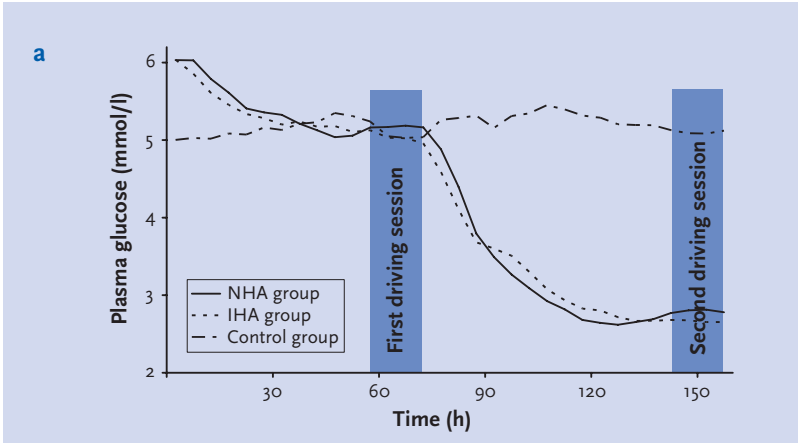
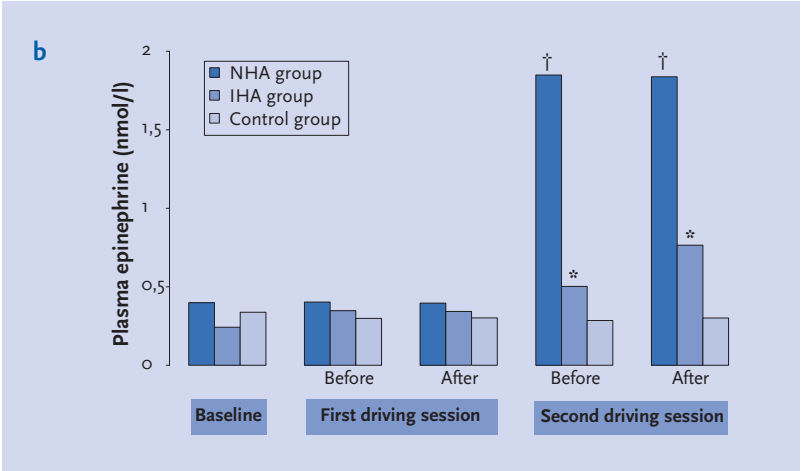
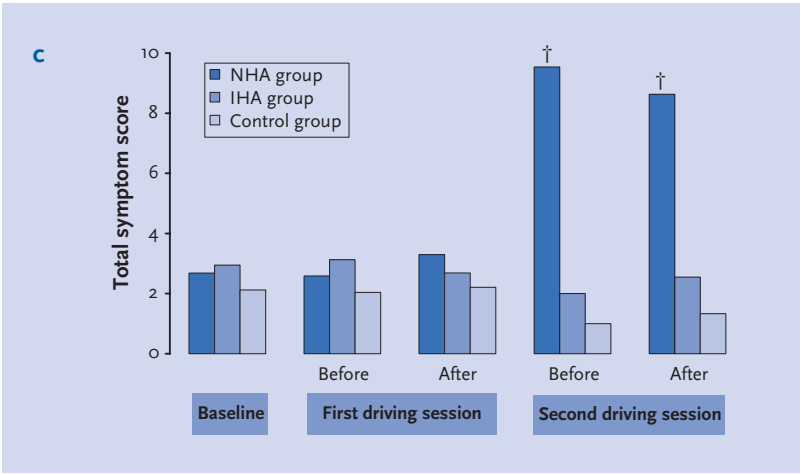


Figure 1a-c. Plasma glucose concentrations, plasma epinephrine concentrations and total symptom scores during the study.





The shaded areas mark the period of the first and second driving session, respectively.
* P=.006 as compared to control group † P<.0001 as compared to control group.

Epinephrine concentrations (FIGURE 1B) at baseline were 0.40 ± 0.35; 0.24 ± 0.24; and 0.34 ± 0.19 nmol/l, in the NHA, IHA and control group, respectively. Before and after the euglycemic runs in all groups, epinephrine concentrations were not significantly different (0.40 ± 0.7 and 0.39 ± 0.24; 0.35 ± 0.32 and 0.34 ± 0.20; 0.30 ± 0.22 and 0.29 ± 0.35 nmol/l in the NHA, IHA and control group, respectively).

Epinephrine concentrations increased significantly before and after the hypoglycemic runs in the NHA group (1.85 ± 1.56 and 1.84 ± 1.29 nmol/l; P<.0001), and slightly, but significantly, in the IHA group (0.50 ± 0.43 and 0.77 ± 0.71 nmol/l; P=.006). There was no rise in epinephrine concentrations in the control group (remaining euglycemic) (0.29 ± 0.35 and 0.30 ± 0.33 nmol/l; P=.91) All symptom scores (autonomic, neuroglycopenic and total scores) were low at baseline, and before and after the euglycemic runs in all groups (Figure 1c). There were no significant differences between these scores. As expected, total symptom scores increased in the NHA group, to 9.5 ± 6.2 and 8.6 ± 6.5 (P<.0001) before and after hypoglycemic driving. During the second driving session, there were no significant changes in either autonomic, neuroglycopenic or total symptom scores, in the IHA group (hypoglycemia) nor in the control group (euglycemia).

Driving performance and PDT

Data of individual parameters of driving performance and PDT are shown in Table 1.

Because of the large amount of parameters, on the rural road and in built-up areas only two parameters are shown. However, when a significant difference was found with ANOVA as compared to the control group, z-scores were calculated for all parameters.

During euglycemia, patients with NHA performed significantly better on critical situations on the highway, but not in any other situation. When a composite z-score was calculated, the magnitude of this effect proved to be very small (+0.10). Similarly, subjects with IHA performed better during uneventful driving on the rural road and during some critical situations in built-up areas. Again, these differences were, although statistically significant, of very small magnitude, as indicated by composite z-scores of +0.11 and +0.02, respectively. Driving performance of patients with NHA and IHA did not deteriorate during moderate hypoglycemia. In a number of situations performance was even better as compared to healthy controls, but the composite z-scores were close to zero (+0.10, +0.04 and +0.02 for the NHA group and +0.02 for the IHA group, respectively), and therefore these effects seem negligible (Table 2).

Reaction time on the PDT signal was significantly longer in the NHA and IHA group during narrow curves in built-up areas, and in wide curves on the rural road for the IHA group. However, the composite z-scores were very small (-0.19, -0.07 and -0.15, respectively). Moreover, in all other driving situations there was no significant difference in PDT performance between NHA and IHA patients and healthy controls. Therefore, workload of patients in both diabetic groups appears to be increased minimally or not at all. When patients were hypoglycemic, a similar pattern was observed. PDT reaction time of both patient groups was longer in critical situations on the rural road (composite z-scores -0.07 and -0.08, respectively), and for the IHA group also during uneventful driving on the rural road (z-score -0.18) (Table 2).
Discussion

Table 1. Driving parameters during uneventful driving and critical situations

Driving situation	Parameter	First driving session		
		NHA	IHA	Controls
Highway				
Uneventful driving	Average speed (m/s)	28.21	28.45	29.41
Approaching impediment		21.84	22.22	23.73
Uneventful driving	Left lane crossing (%t)	14.9	13.3	15.7
Approaching impediment		15.9	17.7	31.0
Uneventful driving	Right lane crossing (%t)	3.7	3.9	3.4
Approaching impediment		3.0	1.0	0.3
Uneventful driving	Reaction time PDT (s)	0.677	0.686	0.653
Approaching impediment		0.742	0.867	0.836
Uneventful driving	MIssed PDT (%)	11.4	11.9	11.5
Approaching impediment		42.0	47.3	42.6
Rural road				
Uneventful driving	Average speed (m/s)	21.75	21.57	21.88
Wide curve		21.99	21.94	22.28
Overtaking		17.20	17.63	17.05
Uneventful driving	Left lane crossing (%t)	4.9	2.7	3.3
Wide curve		5.6	3.9	4.9
Overtaking		33.4	39.2	34.3
Uneventful driving	Right lane crossing (%t)	2.0	2.5	2.4
Wide curve		2.0	1.6	1.6
Overtaking		0.0	0.0	0.0
Uneventful driving	Reaction time PDT (s)	0.662	0.675	0.654
Wide curve		0.676	0.667	0.661
Overtaking		0.843	0.923	0.813
Uneventful driving	Missed PDT (%)	7.8	7.7	5.4
Wide curve		8.1	8.3	6.5
Overtaking		21.1	33.9	17.5
Built-up areas				
Uneventful driving	Average speed (m/s)	20.48	20.04	20.68
Narrow curve		12.08	11.97	12.30
Crossing pedestrian/car		12.32	12.31	13.43
Uneventful driving	Left lane crossing (%t)	0.0	0.0	0.3
Narrow curve		10.6	11.4	14.7
Crossing pedestrian/car		0.2	0.0	1.1
Uneventful driving	Right lane crossing (%t)	0.3	0.6	0.7
Narrow curve		10.9	8.8	9.0
Crossing pedestrian/car		0.7	0.0	0.0
Uneventful driving	Reaction time PDT (s)	0.690	0.686	0.670
Narrow curve		0.849	0.796	0.731
Crossing pedestrian/car		0.951	0.881	0.835
Uneventful driving	Missed PDT (%)	8.8	9.3	7.2
Narrow curve		17.2	15.5	14.9
Crossing pedestrian/car		45.0	53.2	39.8

* Uneventful driving: straight driving, no specific actions demanded. (%t): percentage of time. Analysis of variance (ANOVA) was applied to test for effects of study group versus controls (Group) as well as for effects of hypoglycemic versus euglycemic conditions (Group*Trial).

Second driving session			Euglycemia (Group)		Hypoglycemia (Group*Trial)	
NHA	IHA	Controls	P(NHA)	P(IHA)	P(NHA)	P(IHA)
27.24	27.59	27.74	.25	.47	.72	.64
20.60	9.70	21.02	.16	.14	.64	.95
14.6	12.2	14.2	.92	.14	.85	.95
11.8	16.8	17.6	.05	.16	.23	.19
3.9	4.7	4.4	.88	.54	.51	.92
0.6	0.8	0.0	.14	.19	.36	.92
0.693	0.721	0.666	.23	.09	.88	.23
0.787	0.840	0.714	.84	.15	.06	.34
15.1	14.4	10.5	.31	.32	.19	.28
42.3	45.0	32.7	.43	.14	.40	.56
21.87	21.89	22.41	.31	.31	.30	.62
22.06	22.28	22.87	.09	.22	.22	.57
16.96	16.56	17.38	.82	.85	.63	.28
3.4	2.0	4.3	.70	.04	.04	.21
3.8	3.6	7.3	.34	.11	.04	.19
19.2	22.3	33.2	.15	.57	.54	.51
2.6	3.1	1.8	.62	.39	.10	.44
1.9	1.2	1.6	.59	.71	.98	.72
0.0	0.0	0.0	n.a.	n.a	n.a.	n.a.
0.673	0.685	0.619	.19	.07	.06	.05
0.698	0.696	0.637	.16	.22	.02	.02
0.807	0.855	0.842	.96	.19	.31	.31
6.9	6.4	4.9	.21	.19	.85	.67
9.7	10.1	6.3	.23	.09	.27	.33
25.1	36.1	27.2	.92	.04	.51	.40
20.83	20.64	21.50	.27	.13	.24	.59
12.35	12.24	13.14	.17	.09	.03	.04
12.22	11.89	12.83	.11	.04	.29	.74
0.1	0.0	0.5	.13	.12	.46	.40
9.9	13.9	13.2	.24	.68	.78	.12
0.0	0.3	0.5	.09	.15	.62	.29
0.8	0.0	0.2	.90	.71	.36	.92
10.7	11.8	12.9	.95	.79	.22	.78
1.0	0.0	0.0	.06	n.a.	.70	n.a.
0.715	0.695	0.646	.09	.14	.16	.25
0.807	0.796	0.684	.00	.02	.91	.29
0.900	0.954	0.809	.06	.08	.81	.25
9.7	9.5	5.4	.23	.13	.41	.41
18.4	10.3	12.9	.48	.82	.51	.54
50.0	50.1	36.7	.25	.08	.37	.99

Table 2. Composite z-scores of driving performance and peripheral detection task during euglycaemia and hypoglycaemia as compared to healthy controls*

Driving situation	Normal Hypoglycemia Awareness Group			
	Driving Performance		Peripheral Detection Task	
	Euglycemia	Hypoglycemia	Euglycemia	Hypoglycemia
Highway				
Uneventful driving	0	0	0	0
Critical situations	+0.10	0	0	0
Rural road				
Uneventful driving	0	+0.10	0	0
Critical situations	0	+0.04	0	-0.07
Built-up areas				
Uneventful driving	0	0	0	0
Critical situations	0	+0.02	-0.19	0

* Values are composite z-scores (standardize effect size) versus healthy controls. Z-score was calculated when a statistically significant difference was found with ANOVA as compared to healthy controls. 0 signifies that no statistically significant difference was found. Uneventful driving: straight driving, no specific actions demanded. Critical situations: specific actions demanded, e.g. steering, braking et cetera. Values are averages of all

This is the first study to examine driving performance during prolonged hypoglycemia, allowing for appropriate data collection, and using a high-fidelity driving simulator. We have shown that patients with type 1 diabetes mellitus, with either normal or impaired hypoglycemia awareness, can drive safely during euglycemia and moderate hypoglycemia (2.7 mmol/l). The driving results during euglycemia were consistent with normal and safe driving behavior. If any effect was to be noted, patients appeared to drive better than the control groups. However, the effects of differences found, although statistically significant, were very small, and did not show a consistent pattern. During moderate hypoglycemia, which was symptomatic in the NHA group and asymptomatic in the IHA group, driving performance did not deteriorate.

It has previously been shown that the PDT, is a sensitive measure of the amount of effort needed to drive, or 'workload'[28-31]. During euglycemia, both groups of type 1 diabetic patients had significantly poorer PDT-results in critical situations in built-up areas, indicating that they needed more effort to drive safely. Indeed, this is the most demanding task environment. However, composite z-scores did not exceed -0.20 for these results, indicative of very minor effects. One can therefore argue the relevance of these differences. Reasons for an increase in effort needed to drive are unclear. Despite the increased workload, or perhaps for that very reason, safe driving was maintained throughout euglycemia and hypoglycemia for a prolonged period of time.

Impaired Hypoglycemia Awareness Group			
Driving Performance		Peripheral Detection Task	
Euglycemia	Hypoglycemia	Euglycemia	Hypoglycemia
0	0	0	0
0	0	0	0
+0.11	0	0	-0.18
0	0	-0.07	-0.08
0	0	0	0
+0.02	+0.02	-0.15	0

uneventful driving and critical situations, respectively. Commonly used labels for standardized effect sizes that may assist in their interpretation are 'small' (z = 0.20-0.50), 'moderate' (z = 0.50-0.80) and 'large' (z >0.80)48. controls. 0 signifies that no statistically significant difference was found. Uneventful driving: straight 'small' (z = 0.20-0.50), 'moderate' (z = 0.50-0.80) and 'large' (z >0.80)[48].

Previously, several studies have addressed accident rates in patients with diabetes[3-16]. Results from these studies vary considerably, and their validity is questionable. Many of these studies are dated, conducted before the era of strict metabolic control. All studies are retrospective, relying on databases or on self-reports, and reasons of accidents are not specified. Often, study populations are selected, while no distinction is made between type 1 and type 2 diabetes, and control groups are absent or are not well matched. The state of hypoglycemia awareness has not been taken into account in any study. Moreover, accident studies do not specify whether accidents were directly related to diabetes, and do not correct for exposition to potentially dangerous traffic (e.g. a person can avoid driving on unfamiliar roads or in the dark). Therefore, these studies principally indicate whether self-corrective behavior is effective, rather than indicating driving performance as such. Previously, two simulator studies have been performed, concluding that mild (4.0-3.4 mmol/l) to moderate (3.4-2.6 mmol/l) hypoglycemia disrupted driving performance[49,50]. However, whereas the data on the decision to drive and to self-treat during hypoglycemia are very interesting, one could argue whether these studies were properly designed to evaluate driving performance. In these studies a fixed-base, low-fidelity, non-mock-up driving simulator was used, providing no interaction with other traffic. In contrast, we studied driving during a prolonged period of time at a stable plasma glucose level, both euglycemic and hypoglycemic, allowing sufficient and representative data collection. Subjects were undisturbed while driving, and were not allowed to discontinue driving. Patients with normal and impaired hypoglycemia awareness were studied separately, and awareness

was objectively confirmed with epinephrine levels and symptom scores. Most importantly, we used a well-matched control group, allowing correction for possible learning effects or deterioration of driving performance over the duration of the study.

The current study meets certain limitations. Driving performance, assessed using a driving simulator, relies on comparative measurements. Thus, it cannot be claimed that simulator results have absolute validity, but only that differences that are found between conditions or groups represent differences that exist in reality. Therefore, it is an indirect measure of the relative risk of road traffic accidents. However, it is well established that there is a close relation between performance in the driving simulator and on the road[29,30,33,41-47], and the driving simulator used in this study is highly validated[33-36]. Furthermore, patients experienced prolonged hypoglycemia at a stable plasma glucose level, which is not a physiological situation. However, this design enabled longer, more accurate data collection in patients who had sustained hypoglycemia[51,52]. Consequently, this experiment was not designed to study the decision to stop driving or to self-treat while hypoglycemic.

The results from this study appear to contradict a large body of evidence, showing that cognitive dysfunction occurs during hypoglycemia[21-23]. The cognitive function tests used in these studies are clinical experiments, specifically designed to explore a specific element, or group of elements, of cognition. Driving, on the other hand, is a complex, everyday operation with multiple aspects, requiring mental alertness; visual, auditory and kinesthetic information processing; eye-hand coordination; and manual dexterity. In addition, it is to a certain extent depending on automatisms. Therefore, these results are not necessarily in contradiction with current knowledge about hypoglycemia.

It is of no doubt that when plasma glucose levels decrease to lower levels than studied, driving performance eventually will be affected. It is not clear at which level of glycemia these decrements will occur, and levels may even vary between subjects. Ethical standards prevent the study of these conditions. Nonetheless, the current results suggest that patients with type 1 diabetes with good awareness of hypoglycemia (±75% of patients)[19,20] have a so called 'window of action', i.e. a lag time between occurrence of warning symptoms and onset of impaired driving performance. The possible occurrence of hypoglycemic events during driving in patients with normal awareness of hypoglycemia therefore does not imply a risk per se, but the decision to take adequate action (pull over and consume carbohydrates) is crucial. Avoidance of hypoglycemia during driving remains of paramount importance, and thorough patient education is needed. However, in patients with impaired hypoglycemia awareness, this window of action will be more narrow or even absent, making these patients more at risk for suffering driving decrements, possibly leading to traffic incidents, even when well educated and responding adequately when symptoms of hypoglycemia occur. This problem may increase substantially in the near future, as a growing proportion of patients is treated with intensive insulin regimens, potentially leading to reduced hypoglycemia awareness, and an increased risk of severe hypoglycemia[53-55].

In conclusion, patients with type 1 diabetes drove safely under euglycemic conditions, although perhaps slightly more effort was needed. However, the fact that driving performance was maintained must by itself be considered to be of primary importance. Moderate hypoglycemia (2.7 mmol/l) did not influence driving performance or workload, thus allowing patients with normal hypoglycemia awareness to take appropriate measures when moderate hypoglycemia occurs during driving, before driving performance will inevitably decrease at lower blood glucose levels.

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This work is dedicated to the memory of D.Willem Erkelens (1941-2004).

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Chapter 4 Type 2 diabetes mellitus and driving performance under euglycemic and hypoglycemic conditions

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Abstract

Background

Management of the rising number of patients with type 2 diabetes is progressively aiming at near-normoglycemia, and prevalence of hypoglycemia is increasing.
Although driving privileges are under debate throughout the world, no clear data are available on driving performance or the occurrence of road traffic incidents.

Methods

We studied 20 type 2 diabetic subjects with normal awareness of hypoglycemia, and 24 healthy controls, in a state-of-the-art driving simulator. Driving performance was studied in different environments during clamped euglycemia (90 mg/dL [5.0 mmol/L]) and moderate hypoglycemia (49 mg/dL [2.7 mmol/L]). Various driving parameters were measured. Also, a continuous peripheral detection task was applied to monitor driver's workload. For several subgroups post-hoc analyses were performed.

Results

Driving performance during euglycemia was slightly poorer in the study group for a number of conditions. The magnitude of these effects was very small, with no consistent pattern. Therefore, these decrements do not seem practically relevant. During hypoglycaemia driving performance was not further affected. No subgroup with poorer driving performance could be identified. However, the effort patients needed to drive, was significantly higher during all euglycemic conditions, further increasing during moderate, symptomatic hypoglycemia.

Conclusions

Patients with type 2 diabetes and normal awareness of hypoglycemia drove safely during euglycemia. For reasons unclear, more effort was required to drive safely as compared to non-diabetic drivers. During moderate, symptomatic hypoglycemia safe driving was maintained. Therefore, when hypoglycemia occurs during driving, patients have the opportunity to take proper action before driving performance will inevitably decrease at lower blood glucose levels.

Introduction

Management of the rising number of patients with type 2 diabetes is progressively aiming at near-normoglycemia. Moreover, insulin is used earlier in the course of the disease. Consequently, the incidence of hypoglycemia increases[1]. Prevalence of serious hypoglycemia (requiring outside help) in type 2 diabetes is reported to be 0.5-7.3% per annum, predominantly in patients receiving insulin[2,3].
Current legal restrictions regarding diabetes and driving privileges vary throughout the world. In the USA as well as Europe, driving privileges for patients with diabetes are under debate. However, data on diabetes and driving are conflicting, and, particularly for type 2 diabetes, scarce. Previously, traffic accident rates in cohorts of patients with diabetes have been higher in some studies[4-8]. Other studies show lower accident rates[9,10], while in most studies no differences are reported[11-15]. Validity of these studies, however, is questionable[16,17], and only one study discusses separate results of type 2 diabetic patients[8]. However, accident studies do not specify whether accidents were directly related to diabetes, and they do not correct for exposition to potentially dangerous traffic (e.g. driving on unfamiliar roads or in darkness). Therefore, these studies principally indicate whether self-corrective behavior is effective, rather than indicating driving performance as such. No data on driving performance of patients with type 2 diabetes are available.

A driving simulator is commonly used in traffic psychology and provides the opportunity to apply a standardized test, in which different aspects of driving performance can be measured objectively[18-21]. We performed a study aimed to assess driving performance of type 2 diabetes patients during euglycemia and during moderate, symptomatic hypoglycemia, using a state-of-the-art driving simulator.

Methods

Subjects

Patients were recruited from the outpatient clinic of the University Medical Center Utrecht, the Netherlands. Eligibility criteria included age between 20 and 65 years, at least two years of type 2 diabetes mellitus, glutamic acid decarboxylase antibody negativity, absence of cardiovascular disease or neuropathy, visual acuity >16/20 in both eyes, possession of a driving license for at least two years, and at least 5000 miles driven in the past year. Healthy control subjects were recruited at random from the general population. They met the same eligibility criteria, but could not have diabetes or any other disease potentially interfering with driving performance. No subject could use medication influencing hypoglycemia counter regulation or the ability to drive, or have any experience with the driving simulator. The study was approved by the institutional review board of the University Medical Center Utrecht, and all subjects gave written informed consent.

Driving simulator

To objectively assess driving performance, the Netherlands Organization for Applied Scientific Research (TNO) state-of-the-art driving simulator in Soesterberg, the Netherlands, was used (Figure 1). The driving simulator consisted of several subsystems:

a) A mock-up of a Volvo 240 sedan (automatic gearshift), with all normal instruments at the driver's disposal. Steering wheel and accelerator and braking pedals were equipped with a force-feedback system.
b) The vehicle model computer calculated the position of the vehicle, velocity, and heading, based on the input ("driving") of the subject.
c) The supervisor computer coordinated communication between subsystems, data storage, and behavior of other simulated traffic.
d) A computer generated image system, based on data input from the vehicle model. Images were projected onto a screen (radius 3.75 meters) in front of the mock-up by three high-resolution projectors.
e) The mock-up was equipped with a nearside and offside wing-mirror as well as a rear-view mirror.
f) Sound of the vehicle (engine, wind, tires) and other vehicles was generated with a sampled sound system sampler.
g) The mock-up was situated on a moving base with six degrees freedom in all directions, to realistically simulate road contact, acceleration, deceleration, et cetera.

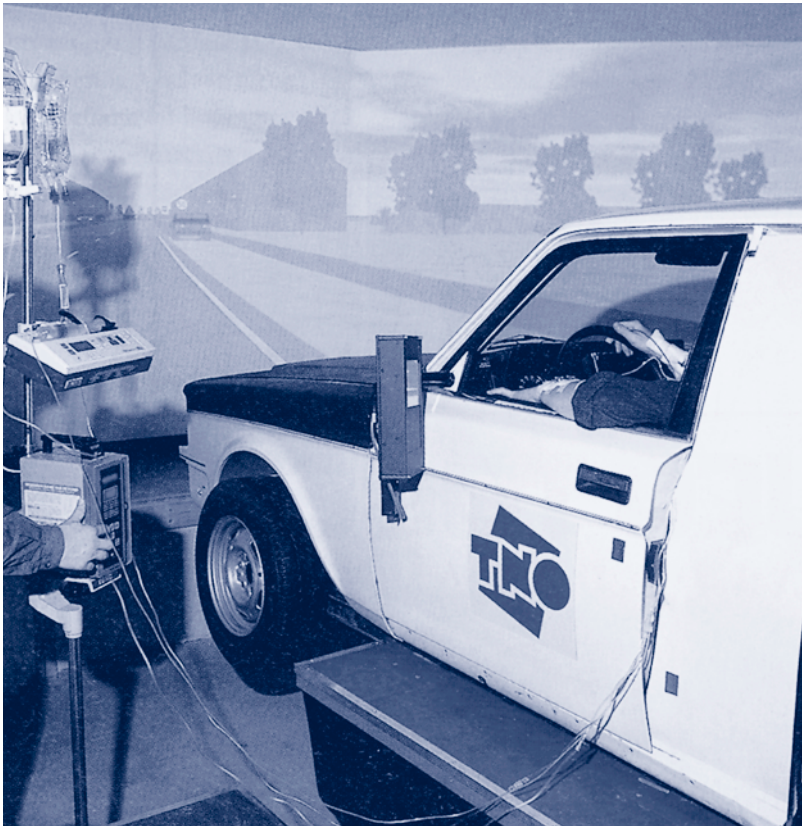
Interaction with other traffic took place at all times.

In addition to driving performance per se, the mental effort needed to obtain a certain level of performance was assessed by having subjects continuously perform the Peripheral Detection Task (PDT), a generally accepted method for estimating workload. A red light stimulus (dot) was presented for one second at a horizontal angle of between 11° and 23° with a random inter-stimulus interval of 3 to 5 seconds. The driver had to respond to the stimulus by pressing a response button attached to

the dominant index finger. The reaction time, as well as the percentage of missed signals, increase with higher driver workload or effort, and thus reflect the effort drivers need to execute the primary driving task[22,23].

Speed, right lane crossing, left lane crossing, PDT reaction time, and missed PDT-signals were measured by the vehicle computer during straight driving (all road types), and during critical situations. Critical situations were: approaching a traffic jam, braking vehicle in front, and package falling of truck (motorway); approaching crossing, overtaking of slow vehicle in front, and wide curve (radius >2000 m) (rural road); narrow curve (radius <500 m), medium curve (radius 500-2000 m), wide curve, pedestrian crossing road, car crossing road, and approaching stop sign (built-up areas). This simulator was previously described24, and has been validated extensively[25-28].

Figure 1. The Netherlands Organization for Applied Scientific Research (TNO) state-of-the-art driving simulator.



Procedure

Patients treated with insulin were withdrawn from long and intermediate acting insulin for 24 hours before the study and managed with short-acting insulin. Patients using oral glucose lowering agents were withdrawn from these agents 24 hours prior to the study. Subjects arrived at 8:00 PM on the evening before the study. Two antecubital veins were cannulated. No caffeinated beverages were consumed. Subjects were given a bedtime snack at 11:00 PM, and remained fasting until the end of the study. In patients, nocturnal near-normoglycemia was maintained, using a variable, low-dose insulin infusion[29]. In the morning, all participants drove a thirty-minute test run to get accustomed to the simulator and minimize learning effects. Subsequently, a hyperinsulinemic glucose clamp was started with insulin (Human Actrapid, Novo Nordisk, Gentofte, Denmark) infused at 2.0 mU/kg/min, and dextrose 20% administered at a variable rate. Arterialized venous blood samples (55 °C) were obtained every 5 minutes, and plasma glucose was measured (YSI 2300 STAT, Yellow Springs Instruments, Yellow Springs, OH, USA). Subjects were blinded for their plasma glucose level.

Subjects completed two sessions of three runs in the driving simulator. Runs lasted minimum 8 minutes, and were staged on a highway, on a rural road, and in built-up areas. There were two scenarios per road type, assigned in a randomized, cross-over fashion. Before and after each run, plasma glucose concentration was checked during a one minute interval, to ensure that the target plasma glucose level was maintained. The first driving session was driven with a plasma glucose concentration of 90 mg/dL (5.0 mmol/L). Subsequently plasma glucose was lowered to 49 mg/dL (2.7 mmol/L) in patients, whereas in control subjects 90 mg/dL (5.0 mmol/L) was maintained. After 60 minutes, the second driving session was performed. Each subject drove a total of at least 48 minutes. Cannulas and intravenous lines did not interfere with any movement required for driving. At baseline and immediately before and after each driving session, blood was drawn to measure epinephrine levels (HPLC-essay, Chromesystems, Munich, Germany). Also, before and after each driving session, subjects rated each of the following hypoglycemic symptoms from 0 (none) to 6 (severe) in a semi-quantitative questionnaire: palpitations, anxiety, tremor, sweating, cold hands, numb lips, dry mouth (autonomic symptoms); difficulty concentrating, blurred vision, impaired speech, confusion (neuroglycopenic symptoms); difficulty breathing, painful legs, seeing yellow halos (dummy symptoms).

Statistical analysis

The experiment was powered to detect minute differences in driving performance. For 80% power at z=0.2, a group size of 18 would be required. Test-retest correlation was assumed to be 0.95[30,31].

Analysis of variance (ANOVA) was applied to test for main effects of study group versus controls, as well as for the hypoglycemic versus euglycemic conditions, corrected for learning or fatigue effects during the second run (Group*Trial interaction). α (one-sided) was 0.05.

To allow interpretation of the large amount of data, it is common practice to create composite parameters of driving performance and PDT,[25-28,32-35]. For this purpose, the magnitude of effect was estimated for all effects that were significant at the 0.05 level. Standardized difference scores (z-scores) were calculated, defined as the difference between the average scores of two groups, divided by their common standard deviation[36]. If the effect was not significant, the z-score was 0. Thus, for each separate parameter, a z-score for straight (uneventful) driving was obtained, and various z-scores for critical situations. The average z-score of all critical situations was calculated. Subsequently z-scores of driving parameters and PDT parameters were averaged. For driving, even weight was given to average speed, right lane crossing and left lane crossing. For workload even weight was given to PDT reaction time and missed PDT signals. As a result, composite z-scores were achieved for driving performance and PDT during uneventful driving and critical situations. Commonly used labels for standardized effect sizes that may assist in their interpretation are 'small' (z = 0.20-0.50), 'moderate' (z = 0.50-0.80) and 'large' (z >0.80)[36]. Post-hoc analyses were performed using Fisher's exact test. Other data will be presented as mean (SD), with a two-sided 5% level of significance in Student's t-tests.

Results

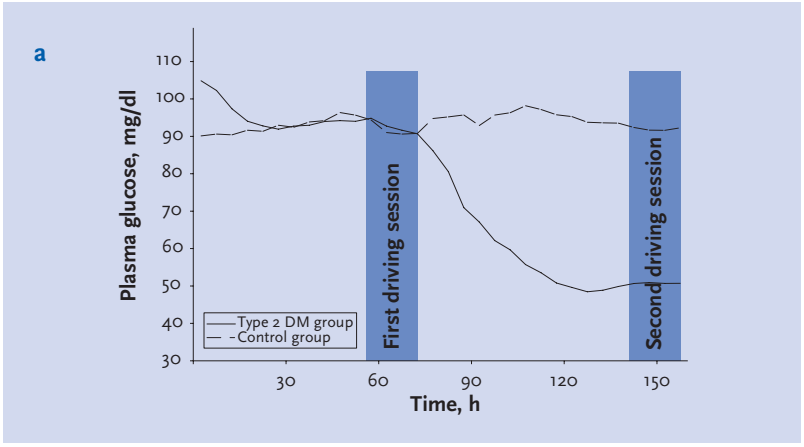
A total of 20 patients with type 2 diabetes mellitus and 24 healthy control subjects were enrolled in the study (Table 1).

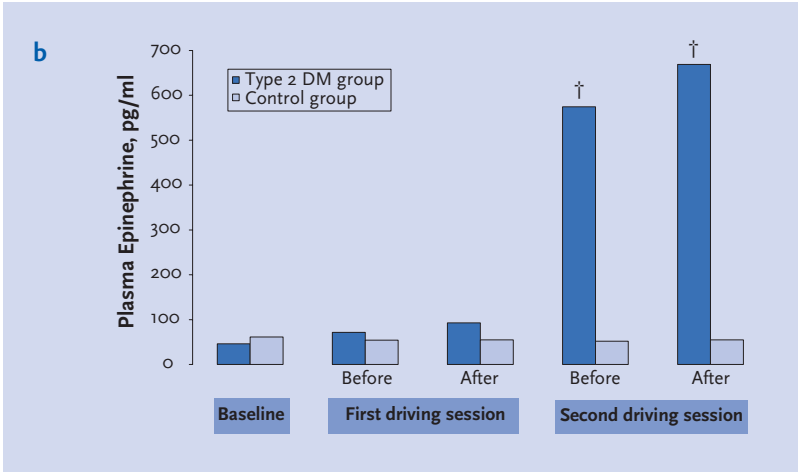
Table 1. Characteristics of Subjects*

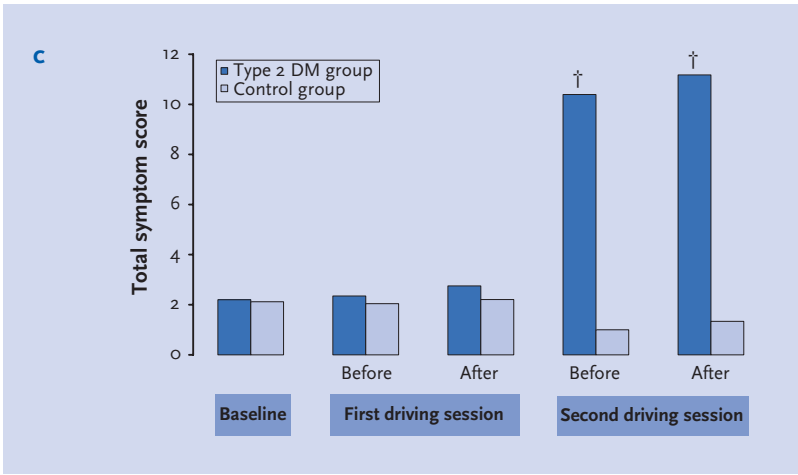
Characteristics	Type 2 diabetes group (n=20)	Control group (n=24)
Age, y	51.6 ± 9.0 †	39.4 ± (2.4)
Sex		
Men, No. (%)	16 (80)	15 (62)
Women, No. (%)	4 (20)	9 (38)
Height, m	1.78 ± 0.08	1.78 ± 0.08
Weight, kg	89.4 ± 14.5 †	77.7 ± 10.5
BMI, kg/m²	28.3 ± 4.0 †	24.5 ± 3.2
Duration of diabetes, y	8.7 ± 5.3	
HbA_{1C}	7.9 ± 1.6 †	5.39 ± 0.3
Driving license, y	28.6 ± 10.3	18.8 ± 10.2
Miles‡ driven/year	14466 ± 8785	15486 ± 14547

* All values are means ± SD, unless otherwise indicated
† P<.05 for comparison with the control group
‡ To convert miles to kilometers, multiply by 1.609

Figure 2a-c. Plasma glucose concentrations, plasma epinephrine concentrations and total symptom scores during the study.







The shaded areas mark the period of the first and second driving session, respectively.
† P<.0001 as compared to control group. To convert mg/dL to mmol/L, multiply by 0.0551. To convert pg/mL to pmol/L, multiply by 5.458.

Glucose clamp

During the first driving session plasma glucose concentrations were maintained at 90±13 mg/dL (5.02±0.74 mmol/L) in both groups (P=0.99). During the second driving session plasma glucose concentrations were lowered to 50±5 mg/dL (2.79±0.28 mmol/L) in patients, and maintained at 92±14 mg/dL (5.09±0.76 mmol/L) in controls (P<0.0001) (FIGURE 2A).

Table 1. Driving parameters during uneventful driving and critical situations

Driving situation	Parameter	First driving session	
		Type 2 DM	Controls
Highway			
Uneventful driving	Average speed (m/s)	27.17	29.41
Critical situations		20.77	23.73
Uneventful driving	Left lane crossing (%t)	12.0	15.7
Critical situations		14.2	31.0
Uneventful driving	Right lane crossing (%t)	3.8	3.4
Critical situations		3.4	0.3
Uneventful driving	Reaction time PDT (s)	0.675	0.653
Critical situations		0.820	0.836
Uneventful driving	Missed PDT (%)	12.7	11.5
Critical situations		47.5	42.6
Rural road			
Uneventful driving	Average speed (m/s)	21.52	21.88
Wide curve		21.91	22.28
Overtaking		18.12	17.05
Uneventful driving	Left lane crossing (%t)	4.4	3.3
Wide curve		9.8	4.9
Overtaking		47.4	34.3
Uneventful driving	Right lane crossing (%t)	1.7	2.4
Wide curve		3.1	1.6
Overtaking		0.0	0.0
Uneventful driving	Reaction time PDT (s)	0.671	0.654
Wide curve		0.672	0.661
Overtaking		0.754	0.813
Uneventful driving	Missed PDT (%)	8.5	5.4
Wide curve		10.3	6.5
Overtaking		40.4	17.5
Built-up areas			
Uneventful driving	Average speed (m/s)	20.38	20.68
Narrow curve		11.47	12.30
Crossing pedestrian/car		12.95	13.43
Uneventful driving	Left lane crossing (%t)	0.4	0.3
Narrow curve		12.1	14.7
Crossing pedestrian/car		2.0	1.1
Uneventful driving	Right lane crossing (%t)	0.6	0.7
Narrow curve		9.7	9.0
Crossing pedestrian/car		0.0	0.0
Uneventful driving	Reaction time PDT (s)	0.701	0.670
Narrow curve		0.807	0.731
Crossing pedestrian/car		0.871	0.835
Uneventful driving	Missed PDT (%)	10.5	7.2
Narrow curve		15.8	14.9
Crossing pedestrian/car		48.0	39.8

* Uneventful driving: straight driving, no specific actions demanded. (%t): percentage of time. Analysis of variance (ANOVA) was applied to test for effects of study group versus controls (Group) as well as for effects of hypoglycemic versus euglycemic conditions (Group*Trial).

Second driving session		Euglycemia (Group)	Hypoglycemia (Group*Trial)
Type 2 DM	Controls	P	P
27.09	27.74	.08	.39
22.10	21.02	.34	.21
12.1	14.2	.07	.79
14.8	17.6	.06	.13
5.0	4.4	.49	.87
2.2	0.0	.05	.54
0.726	0.666	.05	.08
0.929	0.714	.06	.03
17.1	10.5	.07	.18
43.6	32.7	.15	.66
22.44	22.41	.74	.48
22.90	22.87	.74	.51
16.16	17.38	.90	.06
8.3	4.3	.08	.10
15.2	7.3	.03	.36
27.0	33.3	.53	.43
3.4	1.8	.33	.01
2.3	1.6	.19	.51
0.0	0.0	n.a.	n.a.
0.735	0.619	.01	.00
0.713	0.637	.11	.00
0.791	0.842	.25	.92
13.6	4.9	.01	.05
13.0	6.3	.04	.28
41.7	27.2	.03	.38
20.73	21.50	.24	.38
12.12	13.14	.02	.58
13.04	12.83	.83	.31
0.7	0.5	.57	.71
12.6	13.3	.65	.52
3.3	0.5	.06	.40
1.3	0.2	.40	.36
12.7	12.9	.93	.82
0.0	0.0	n.a.	n.a.
0.714	0.646	.07	.30
0.783	0.684	.02	.59
0.941	0.809	.28	.29
14.7	5.4	.02	.07
22.4	12.8	.29	.21
53.5	36.7	.12	.38

Epinephrine concentrations and symptom scores

To verify that patients truly experienced symptomatic hypoglycemia during the second driving session, epinephrine concentrations and symptom scores were assessed.

Epinephrine concentrations are shown in FIGURE 2B. Epinephrine concentrations increased significantly before and after the hypoglycemic runs in the study group (3160±2670 and 3680±2510 pmol/L [575±485 and 669±457 pg/mL]; P<0.0001). There was no rise in epinephrine concentrations in the control group (290±350 and 300±330 pmol/L [52±64 and 55±59 pg/mL]; P=0.91).
Symptom scores are shown in FIGURE 2C. As expected, total symptom scores increased in the study group to 10.4±5.6 and 11.2±7.0 (P<0.0001) before and after hypoglycemic driving. During the second driving session, no significant changes in symptom scores occurred in the control group (euglycemia).

Driving performance and PDT

Driving performance and PDT are shown in TABLE 2. Because of the large amount of parameters, on the rural road and in built-up areas only two parameters are shown. However, when a significant difference was found with ANOVA as compared to the control group, z-scores were calculated for all parameters.
Driving performance during euglycemia was significantly poorer in the study group during critical situations on the motorway and on the rural road (TABLE 3). However,

Table 3. Composite z-scores of driving performance and peripheral detection task during euglycaemia and hypoglycaemia as compared to healthy controls*

Driving situation	Driving Performance		Peripheral Detection Task	
	Euglycemia	Hypoglycemia	Euglycemia	Hypoglycemia
Highway				
Uneventful driving	0	0	-0.16	0
Critical situations	-0.11	0	0	-0.38
Rural road				
Uneventful driving	0	-0.14	-0.56	-0.43
Critical situations	-0.05	0	-0.23	-0.21
Built-up areas				
Uneventful driving	0	0	-0.24	0
Critical situations	+0.03	-0.03	-0.28	0

* Values are composite z-scores (standardize effect size) versus healthy controls. Z-score was calculated when a statistically significant difference was found with ANOVA as compared to healthy controls. 0 signifies that no statistically significant difference was found. Uneventful driving: straight driving, no specific actions demanded. Critical situations: specific actions demanded, e.g. steering, braking et cetera. Values are averages of all uneventful driving and critical situations, respectively. Commonly used labels for standardized effect sizes that may assist in their interpretation are 'small' (z = 0.20-0.50), 'moderate' (z = 0.50-0.80) and 'large' (z >0.80)[36].

patients in the study group performed significantly better during critical situations in built-up areas, which is the most demanding task environment. Although statistically significant, when a composite z-score was calculated, the magnitude of all these effects proved to be very small (z=-0.11; z=-0.05; and z=+0.03, respectively). Driving performance in other environments during euglycemia was neither better nor worse than in the control group. During hypoglycemia driving performance was not affected, except during uneventful driving on the rural road and in critical situations in built-up areas. Again, these differences were of very small magnitude, (composite z-scores of -0.14 and -0.03, respectively).

In the study group, the effort needed to drive, as expressed in PDT-results, was significantly higher in virtually all euglycemic conditions, except for critical situations on the highway (TABLE 3). Composite z-scores exceeded -0.20 for uneventful driving and critical situations on the rural road and in built-up areas, particularly during uneventful driving on the rural road, where the composite z-score was -0.56, demonstrating a moderate effect. Workload increased further during hypoglycemia for critical situations on the highway and uneventful as well as critical situations on the rural road, with composite z-scores of -0.38, -0.43 and -0.21, respectively.

Post-hoc analyses

To identify subgroups with poorer driving performance, post hoc tests were performed using Fisher's exact test for medians. No differences were found in patients using insulin (n=12) compared to patients exclusively using oral glucose lowering agents (n=8). When comparing relatively younger patients (n=10; age=44.9±6.5 years) to older patients (n=10; age=58.2±5.7 years), unexpectedly, the older subgroup appeared to drive more safely and carefully (slower; smaller standard deviation of the lateral position; fewer left and right lane crossing; larger time to line crossing), particularly on the motorway. On the rural road and in built-up areas the same trend was found. Because of the small number of patients who were known for retinopathy and/or laser coagulation of the retina (n=3), post-hoc analysis could not be performed. No differences could be detected between patients with relatively short duration of diabetes (n=9; duration=3.9±1.4 years) versus patients with prolonged duration of diabetes (n=11; duration=12.6±3.6 years).

Discussion

This is the first study to examine driving performance in patients with type 2 diabetes mellitus. We have shown that these patients had normal and safe driving performance during euglycemia, although more effort was required to do so. In a number of situations, decreased driving performance was found, but the effects were of very small magnitude, with no consistent pattern. Therefore these decrements seem, although statistically significant, not practically relevant and negligible. Conversely, there was a clear pattern of an increased workload (PDT) of patients with type 2 diabetes during driving under euglycemic conditions. Moreover, during moderate, symptomatic hypoglycemia, safe driving was maintained, at the expense of an additional increase in attention required.

Several possible factors confounding the current results have been considered: On average, patients in the study group were almost 12 years older than in the control group. If any influence of age was to be expected in the type 2 diabetic subjects, it would be a negative effect. It is well known that driving performance deteriorates with increasing age, although there may be a large variation as to the age and rate of decline[37]. Conversely, in the study group, the older drivers appeared to drive more carefully and more safely, particularly on the motorway. On the rural road and in built-up areas the same trend was found. There were no differences in reaction time to the PDT or percentage of missed signals. Age therefore does not appear to have influenced current results. Similarly, post hoc analyses indicated no influence of either insulin therapy, used by approximately half of the patients in this study, or duration of diabetes.

Where there were little differences in driving performance, surprisingly marked deteriorations were found in the PDT, a sensitive measure of the amount of effort needed to drive, or 'workload'[22,23]. Performance of this task is, in addition to attention needed for driving, dependent of peripheral vision and reaction time. All diabetic subjects visited an ophthalmologist regularly, but only three patients were known to have diabetic retinopathy and/or laser treatment performed. All subjects had good visual acuity. Due to the small number of patients with retinopathy, a post-hoc analysis could not be performed, but for this very reason, it is unlikely that retinopathy has influenced PDT results. Although none of the patients had clinical signs of neuropathy, subclinical neuropathy could possibly account for part of the differences. One could also hypothesize that, as type 2 diabetes influences the brain similarly to aging[38,39], type 2 diabetic patients require more effort to drive safely. Conversely, in this study the older subgroup performed slightly better than the younger subgroup, and no influence of duration of diabetes was found.

The current study meets certain limitations. Driving performance, assessed using a driving simulator, relies on comparative measurements and is an indirect measure of the relative risk of road traffic accidents, also because it does not take self-correcting behavior into account. Thus, it cannot be claimed that simulator results have absolute validity. Nonetheless, it is well established that there is a close relation between

performance in the driving simulator and on the road[22,25,32-35], and the driving simulator used in this study is highly validated[25-28]. Furthermore, in our study patients experienced sustained hypoglycemia. However, hypoglycemic symptoms and counter regulation persisted throughout the second driving session[40,41], enabling longer, more accurate data collection. Finally, patients with diabetic complications, high age or reduced awareness of hypoglycemia have been excluded from the study, and no statements can be made on driving performance in these subgroups. In post-hoc analyses within the diabetic population studied, no subgroups with poorer driving performance could be identified.

The current results suggest that, in patients with type 2 diabetes and normal awareness of hypoglycemia, the possible occurrence of hypoglycemia during driving does not imply a risk per se, for there appears to be a so called 'window of action', i.e. a lag time between occurrence of warning symptoms and onset of impaired driving performance. As driving performance will inevitably deteriorate at lower levels of glycemia, the decision to initiate driving or to take appropriate action during driving (pull over and consume carbohydrates) when hypoglycemic, is of paramount importance. All diabetic drivers should be made aware of the possibility of a hypoglycemic event during driving, and be thoroughly educated regarding prevention and proper action. Also, the importance of frequent blood glucose control before driving, and during longer drives, should be emphasized. To provide more exact data on the relative risk and severity of road traffic accidents in patients with diabetes and numerous subgroups, a large, prospective study with a well-matched control group should be performed.

In conclusion, patients with type 2 diabetes and normal awareness of hypoglycemia drove safely during euglycemia. For reasons unclear, more effort was needed to accomplish this as compared to non-diabetic drivers. However, the fact that driving performance was maintained must by itself be considered to be of primary importance. The effort needed to drive further increased during moderate, symptomatic hypoglycemia, but safe driving was maintained. No subgroup with poorer driving performance could be identified. These results suggest that when hypoglycemia occurs during driving, patients have the opportunity to take proper action before driving performance will inevitably decrease at lower blood glucose levels.

Author Contributions Dr. Stork had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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This work is dedicated to the memory of D.Willem Erkelens (1941-2004).

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Chapter 5 The decision not to drive during hypoglycemia in patients with type 1 and type 2 diabetes, according to hypoglycemia awareness

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Abstract

Background

In recent years, there has been an ongoing discussion on the relationship between diabetes and driving. As driving performance will inevitably decline at lower levels of glycemia, patients' decision concerning driving or taking corrective action when hypoglycemia occurs immediately before or during driving, seems paramount.

Methods

Twenty-four type 1 diabetic patients with normal awareness of hypoglycemia (NHA1), 21 type 1 patients with impaired awareness of hypoglycemia (IHA1) and 20 type 2 patients with normal awareness of hypoglycemia (NHA2) and 24 controls were studied. They were asked whether they felt hypoglycemic and whether they would currently drive during experimental euglycaemia (5.0 mmol/l) and hypoglycemia (2.7 mmol/l).

Results

In the NHA1-group 1 patient (4.2%) decided to drive during hypoglycemia. In the IHA1-group 9 patients (42.9%) said they would drive in the hypoglycemic condition. In the NHA2-group 5 patients (25%) would drive. This was more frequently the case for patients on oral hypoglycemic agents (χ^2=4.44; P=0.04). No effect of gender (χ^2=0.78; P=0.38) or age (χ^2=0.22; P=0.64) was noted.

Conclusions

Patients with type 1 diabetes and impaired awareness of hypoglycemia frequently decide to drive while hypoglycemic, while patients with type 1 diabetes and normal awareness of hypoglycemia appear to make safe decisions concerning hypoglycemia and driving. Strikingly, patients with type 2 diabetes and normal hypoglycemia awareness frequently take potentially dangerous decisions as well, particularly when using oral hypoglycemic agents. Therefore early, clear and consistent education is imperative.

Introduction

In recent years, there has been an ongoing discussion on the relationship between diabetes and driving, since (severe) hypoglycemia may impair driving performance, and thus traffic violations and accidents may occur[1]. Indeed, the group of Cox et al. has shown disrupted driving performance even at glycemic levels of 4.0-3.4 mmol/l[2,3], As driving performance will inevitably decline at low levels of glycemia, patients' decision concerning driving or taking corrective action when hypoglycemia occurs immediately before or during driving, seems paramount. The decision to drive may be complicated by the fact that hypoglycemia induces cognitive dysfunction, and therefore decision making may be impaired[4-6].

In previous studies in type 1 diabetic patients under experimental hypoglycemic conditions, only 22% of patients in a driving simulator pulled over or undertook corrective action while driving at 2.2 mmol/l[3]. During hypoglycemia (2.8 mmol/l), 22-38% of the patients judged that they could drive safely[7]. This perception was more frequent among older patients and females. However, in another study, corrective action was only associated with normal awareness of hypoglycemia, and not with age, gender, duration of disease or other disease-related factors[8]. In their natural environment, using hand-held computers, approximately 40% of patients with type 1 diabetes said they would drive when they estimated their own blood glucose at 3.9-3.3 mmol/l, or even below 2.2 mmol/l. With an actual blood glucose below 2.2 mmol/l, 38-47% decided to drive[9]. No distinction was made according to awareness of hypoglycemia. In the only study involving type 2 diabetic patients, 89% of insulin-using (type 1 and type 2) patients answered to a survey that they would stop when experiencing hypoglycemia during driving. However, 60% reported never to test blood glucose before driving or only when experiencing symptoms of hypoglycemia. Twenty-five percent indicated that they considered blood glucose values below 4.0 mmol/l safe for driving10.

In the current study, we aimed to assess the decision to drive during moderate hypoglycemia (2.7 mmol/l) in controlled experimental conditions, objectively verifying hypoglycemia awareness, in patients with type 1 and patients with type 2 diabetes.

Methods

Subjects

All subjects were adults between the age of 20 and 65 years of age, who participated in a larger study on the effect of hypoglycemia on driving performance in a state-of-the-art driving simulator. Patients were recruited from the outpatient clinic of the University Medical Center Utrecht, Utrecht, the Netherlands. Eligibility criteria included at least two years of diabetes mellitus, absence of cardiovascular disease or neuropathy, visual acuity >16/20 in both eyes, possession of a driving license for at least two years, and at least 5000 miles driven in the past year. Healthy control subjects were recruited at random from the general population. They had to meet the same eligibility criteria, but could not have diabetes or any other disease potentially interfering with driving performance. No subject could use medication influencing hypoglycemia counter regulation or the ability to drive. The study was approved by the institutional review board of the University Medical Center Utrecht, and all subjects gave written informed consent.

Procedure

Patients were withdrawn from long- and intermediate acting insulin for 24 hours before the study and managed with short-acting insulin. Subjects arrived at the TNO Human Factors Research Institute at 8:00 PM on the evening before the study. Two antecubital veins were cannulated. No caffeinated beverages were consumed after arrival. Subjects were given a bedtime snack at 11:00 PM, and remained fasting from bedtime until the end of the study. In patients, nocturnal near-normoglycemia was maintained, using a variable, low-dose insulin infusion[11]. In the morning, a hyperinsulinemic glucose clamp was started. Via one cannula insulin (Human Actrapid, Novo Nordisk, Gentofte, Denmark; in a 4% solution of the subject's own plasma in 0.9% saline) was infused at 2.0 mU/kg/min, (IVAC P2000, IVAC Corporation, San Diego, CA, USA) and dextrose 20% (IVAC 560, IVAC Corporation, San Diego, CA, USA) at a variable rate. Via the other cannula, arterialized venous blood samples were obtained every 5 minutes, using a heating sleeve to warm the arm to 55 °C. The cannula was kept patent with 0.9% saline. Plasma glucose was measured using a glucose oxidase method (YSI 2300 STAT, Yellow Springs Instruments, Yellow Springs, OH, USA). Subjects were blinded for their plasma glucose level during the experiment.

Subjects completed two sessions of three runs in the driving simulator, each run lasting a minimum of 8 minutes. The first driving session was driven with a constant plasma glucose concentration of 5.0 mmol/l. Subsequently plasma glucose was lowered to a constant plasma glucose concentration of 2.7 mmol/l in patients, whereas in control subjects a plasma glucose concentration of 5.0 mmol/l was maintained. Upon achieving this plasma glucose concentration, but after at least 60 minutes, the second driving session was performed. At baseline and immediately before each driving session, blood was drawn to measure epinephrine levels (HPLC-essay, Chromesystems, Munich, Germany). Also, before each driving session, two questions

were posed: 1. "Do you currently feel hypoglycemic?", with possible answers being "yes", "no" or "maybe". 2. "Would you currently drive in everyday life?", with possible answers being "yes", "maybe", "no" or "I would first measure my blood glucose". For non-diabetic control subjects the first question was modified to "Do you currently experience any unusual signs?" Answering the second question, healthy controls did not have the option "I would first measure my blood glucose". Subsequently, a semi-quantitative questionnaire was administered to assess hypoglycemic symptoms. Subjects rated each of the following hypoglycemic symptoms from 0 (none) to 6 (severe): palpitations, anxiety, tremor, sweating, cold hands, numb lips and dry mouth (autonomic symptoms); difficulty concentrating, blurred vision, impaired speech, and confusion (neuroglycopenic symptoms); difficulty breathing, painful legs, seeing yellow halos (dummy symptoms).

Statistical analysis

Assessment of hypoglycemia awareness Before data analysis, it was established for each patient whether there was a significant rise in epinephrine levels or symptom scores during hypoglycemia as compared to euglycaemia, defined as exceeding the 95% confidence limit observed during euglycemia, as previously described[12]. Patients were identified as having normal awareness for hypoglycemia, if there was a significant rise in both parameters.

Analysis of the decision to drive In analyzing the question "Would you currently drive in every day life?" the answers "Yes" and "Maybe" while plasma glucose was 2.7 mmol/l (second driving session), were considered potentially dangerous, as patients would (possibly) drive in a hypoglycemic state. In this situation, "No" and "I would first measure my blood glucose", were considered safe, assuming that patients would take corrective action upon measuring a hypoglycemic value. To determine whether there was a significant difference in answers to the questions posed between various study groups, χ^2-tests were performed. Other data will be presented as mean ± SD, with a two-sided 5% level of significance in Student's t-tests.

Results

Subjects and hypoglycemia awareness

Forty-five patients with type 1 diabetes mellitus and 20 patients with type 2 diabetes were enrolled in the study. Subjects were identified as having normal hypoglycemia awareness based on the combined criteria of both epinephrine levels and symptoms scores. Twenty-four of the type 1 diabetic patients were identified as having normal hypoglycemia awareness (NHA1 group), 21 type 1 diabetic patients had impaired hypoglycemia awareness (IHA1 group). All 20 patients with type 2 diabetes had normal hypoglycemia awareness (NHA2 group). Twenty-four healthy control subjects were matched for gender, duration of possession of driving license and miles driven annually (Control group). The type 2 diabetic patients were older than the subjects in the other study groups (Table 1).

Table 1. Subject characteristics*

Group	NHA1	IHA1	NHA2	Controls
Number (m/f)	24 (17/7)	21 (16/5)	20 (16/4)	24 (15/9)
Age (years)	35.27 ± 8,0	40,4 ± 10,8	51,6 ± 9,0 † §	39,4 ± 11,9
Height (m)	1.78 ± 0,10	1,80 ± 0,08	1,78 ± 0,08	1,78 ± 0,08
Weight (kg)	84.4 ± 14.3	80,2 ± 8,6	89,4 ± 14,5 † §	77,7 ± 10,4
BMI	26,5 ± 4,0	24,9 ± 2,9	28,3 ± 4,0 † §	24,5 ± 3,2
DM (years)	14,8 ± 8,0	19,5 ± 10,0	8,7 ± 5,3 §	
HbA_{1C} (%)	8,17 ± 1,00 †	7,80 ± 1,14 †	7,90 ± 1,55 †	5,39 ± 0,28
Driving license (years)	15,0 ± 8,7	20,3 ± 10,3	28,6 ± 10,3 † §	18,8 ± 10,8
Km/year	25458 ± 28945	21450 ± 14849	23275 ± 14135	25347 ± 23833

* All values are means ± SD, unless otherwise indicated
† P<0.01 for the comparison with the NHA1 and IHA1 group
§ P<0.01 for the comparison with the control group

Euglycemia

Before the first driving session all study groups were euglycemic (plasma glucose 5.12 ± 0.6 mmol/l).

NHA1 group When asked whether they felt hypoglycemic, 22 patients in the NHA1 group (91.7%) stated they did not feel hypoglycemic, and 2 (8.3%) answered "Maybe". Yet, in response to the question whether they would currently drive in everyday life, 7 (29.2%) declared they would first measure their blood glucose before driving. Only 1 subject answered "Maybe" to the latter question (4.5%).

IHA1 group Four patients answered "Maybe" to they question about feeling hypoglycemic (19%), and 8 (38.1%) would first measure their blood glucose before driving, whereas 1 subject (4.8%) would "Maybe" drive.

NHA2 group One patient answered he was "Maybe" hypoglycemic (5%), all others answered "No" (95%). Two patients in this group stated they would first measure their blood glucose (10%), and 3 (15%) said they would not drive in their current condition.

Control group None of the subjects experienced unusual symptoms; two subjects stated they would not drive in everyday life (8.3%).

Analysis of the decision to drive During euglycemia, the decision not to drive (or to measure blood glucose before driving) was made more frequently by patients in both the NHA1 (χ^2=4.55; P=0.03) and IHA1 group (χ^2=5.74; P=0.02), as compared to the control group, but not by patients in the NHA2 group (χ^2=2.27; P=0.13). This was particularly the case for patients using insulin (χ^2=5.50; P=0.02), but not for patients using oral hypoglycemic agents (χ^2=0.22; P=0.64).

Hypoglycemia

After the first driving sessions, hypoglycemia was induced with the hyperinsulinemic clamp (2.68 ± 0.29 mmol/l). The subjects' perception of their glycemic condition during hypoglycemia and their decision to drive are shown in TABLE 2.

NHA1 group Fifteen of 24 subjects (62.5%) felt hypoglycemic. None of these subjects stated they would currently drive, but 1 (6.7%) stated "Maybe" he would drive. Three subjects would measure their blood glucose (20.0%) and 11 (73.3%) would not drive. Nine subjects (37.5%) stated they were "Maybe" hypoglycemic. Eight of them (88.9%) would first measure their blood glucose, and one (11.1%) would not drive.

IHA1 group Eight of 21 subjects (38.1%) stated they possibly were hypoglycemic. Five of these 8 subjects (62.5%) wanted to measure their blood glucose before driving, and 3 (37.5%) would not drive. Thirteen patients (61.9%) did not perceive hypoglycemia, 9 of whom (69.2%) acknowledged they would drive in everyday life. Three (23.1%) would measure their blood glucose prior to driving, and 1 subject (7.7%) would not drive.

NHA2 group Of the 20 type 2 diabetic patients (all with normal hypoglycemia awareness), 11 (55.0%) answered that they felt hypoglycemic. Five (45.5%) of these patients would measure their blood glucose, and 6 (54.5%) would not drive at all. Of the 9 patients who stated they "Maybe" experienced hypoglycemia (45%), 3 (33.3%) would drive anyway in everyday life, and 2 (22.2%) would "Maybe" drive. On the other hand, 2 subjects would measure blood glucose and 2 would not drive (22.2%, respectively).

Control group All control subjects were euglycemic (5.12 ± 0.51 mmol/l) before the second driving session. None experienced any unusual signs. Nevertheless, one subject (4.2%) would not drive.

Analysis of the decision to drive The answers "Yes" and "Maybe" were considered unsafe decisions during hypoglycemia, whereas the answers "No" and "I would first measure my blood glucose" were considered safe. Unsafe decisions were made more frequently in the IHA1 group than in the NHA1 group (χ^2= 9.70; P=0.002). Strikingly, the NHA2 patients also made unsafe decisions (decided to drive) more frequently during hypoglycemia than NHA1 patients (χ^2=4.02; P=0.04).

When comparing the NHA2 group to all type 1 diabetic patients there was no difference (χ^2=0.06; P=0.81). In the NHA2 group, patients using oral hypoglycemic agents answered they would make an unsafe decision (drive) during perceived hypoglycemia more frequently than patients using insulin (χ^2=4.44; P=0.04). When comparing NHA2 patients on oral hypoglycemic agents to all insulin users, the same trend was noted, but it did not reach statistical significance (χ^2=3.73; P=0.054).

Table 2. Perception of glycemic condition during hypoglycemia (2.7 mmol/l) and decision to drive (n(%)). Note that controls were euglycemic (5.0 mmol/l), and were asked whether they perceived any unusual signs, not hypoglycemia. They did not have the option to measure their glucose.

Group	n	Do you feel hypoglycemic?	n	(%)	Would you currently drive?	n	(%)
NHA1	24	Yes	15	(62.5)	Drive	0	(0)
					Maybe	1	(6)
					Measure glucose	3	(20)
					Not drive	11	(73)
		Maybe	9	(37.5)	Drive	0	(0)
					Maybe	0	(0)
					Measure glucose	8	(89)
					Not drive	1	(11)
		No	0	(0.0)	Drive	0	(0)
					Maybe	0	(0)
					Measure glucose	0	(0)
					Not drive	0	(0)
IHA1	21	Yes	0	(0.0)	Drive	0	(0)
					Maybe	0	(0)
					Measure glucose	0	(0)
					Not drive	0	(0)
		Maybe	8	(38.1)	Drive	0	(0)
					Maybe	0	(0)
					Measure glucose	5	(63)
					Not drive	3	(38)
		No	13	(61.9)	Drive	9	(69)
					Maybe	0	(0)
					Measure glucose	3	(23)
					Not drive	1	(8)
NHA2	20	Yes	11	(55.0)	Drive	0	(0)
					Maybe	0	(0)
					Measure glucose	5	(45)
					Not drive	6	(55)
		Maybe	9	(45.0)	Drive	3	(33)
					Maybe	2	(22)
					Measure glucose	2	(22)
					Not drive	2	(22)
		No	0	(0.0)	Drive	0	(0)
					Maybe	0	(0)
					Measure glucose	0	(0)
					Not drive	0	(0)
Controls	20	Yes	0	(0.0)	Drive	0	(0)
					Maybe	0	(0)
					Not drive	0	(0)
		Maybe	0	(0.0)	Drive	0	(0)
					Maybe	0	(0)
					Not drive	0	(0)
		No	24	(100.0)	Drive	23	(96)
					Maybe	0	(0)
					Not drive	1	(4)

There was no difference in the decisions made by men and women (χ^2=0.78; P=0.38). Similarly, there was no difference in the decisions made by younger patients (under the mean age) versus older patients (over the mean age) either in all study groups (mean age=41.95 years; χ^2=0.54; P=0.46), or in the NHA2 group separately (mean age =51.6; χ^2=0.07; P=0.79).

Discussion

This is the first study to examine the decision to drive in diabetic patients according to objectively assessed hypoglycemia awareness, and the first experimental study with type 2 diabetic patients. This study led to two important findings. First, a striking finding is that many type 1 diabetes patients with impaired hypoglycemia awareness (43%) failed to decide not to drive during experimental hypoglycemia. As these patients were not conscious of their hypoglycemic condition, which seems comprehensible. However, as this level of hypoglycemia may be associated with impaired driving performance, and hypoglycemia may progress towards lower levels of glycemia, associated with cognitive deterioration, these decisions may lead to dangerous situations in traffic. In the current study, only 1 of 24 patients (4.2%) with type 1 diabetes and normal hypoglycemia awareness chose to drive while (symptomatically) hypoglycemic.

Second, the perhaps most alarming finding pertains to type 2 diabetic patients. In spite of their normal hypoglycemia awareness, 25% of these patients decided to drive while positive or in doubt whether they were hypoglycemic. This was principally the case for patients on oral hypoglycemic agents. This is particularly worrying because of the large and increasing number of patients with type 2 diabetes. Several factors could play a role. First, as patients with type 2 diabetes experience hypoglycemia less frequently than patients with type 1 diabetes, they could be less familiar with the potential dangers. Second, for this very reason, patients may have received less education from doctors and nurses about hypoglycemia and driving, which is often conflicting[13]. These two possible explanations are supported by the fact that mainly patients on oral hypoglycemic agents make potentially dangerous decisions. Third, by the time that patients are diagnosed with type 2 diabetes, they are generally older than type 1 patients, and have driven for several decades. Consequently, their driving behavior has been well established, and therefore will be less affected by social pressure and education[14].

There are indications that, although potentially dangerous decisions were made, the diabetic subjects in the current study were aware of impending hazards. During euglycaemia, 25-43% of patients stated they would not drive without measuring their blood glucose first, or maybe not drive at all. However, this study meets certain limitations. It must be borne in mind that subjects were familiar with the fact that this was a study about diabetes and driving, and perhaps volunteered out of special

attitudes towards driving. Furthermore, in some instances, subjects may have given "socially desired" answers, instead of their true beliefs. Thus, the results in this study may underestimate true percentages of potentially dangerous decisions. Finally, in the analysis the answer "I would first measure my blood glucose" was considered "safe", assuming that patients would take corrective action upon measuring a hypoglycemic value. However, from previous research it is known that patients may consider values far below 4.0 mmol/l safe to engage in driving[10].

In traffic research, the Theory of Reasoned Action[15], later expanded to the Theory of Planned Behavior[16,17] is frequently used, and has been found to predict a range of road user behaviors[14]. Considering the results from the current study, in line with accepted traffic psychology models, decision making of patients with diabetes in relation to hypoglycemia may be positively modified using a number of interventions. Patients should be made aware repeatedly and explicitly of current recommendations for avoidance of hypoglycemia10 by doctors and nurses. This may be done individually, but also in groups, as this influences perceived behavior by others and peer pressure. Moreover, education should be started in an early phase of the disease, before undesired behavior has been established. In patients developing diabetes at later age, established behavior should be taken into account, even though no clear effect of age was demonstrated in the current study. Lastly, Blood Glucose Awareness Training, a patient education program, designed to teach patients to more accurately estimate blood glucose levels, may improve the decision not to drive while hypoglycemic, and reduce the number of road traffic accidents[18-22].

In conclusion, in the current study, most patients with type 1 diabetes and normal awareness of hypoglycemia appear to make safe decisions concerning hypoglycemia and driving. In contrast, patients with type 1 diabetes and impaired awareness of hypoglycemia frequently decide to drive while hypoglycemic, as may be expected. Strikingly, patients with type 2 diabetes and normal hypoglycemia awareness frequently take potentially dangerous decisions as well, particularly when using oral hypoglycemic agents. This is particularly worrying in light of the increasing number of patients. Therefore early, clear and consistent education is imperative.

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This work is dedicated to the memory of D.Willem Erkelens (1941-2004).

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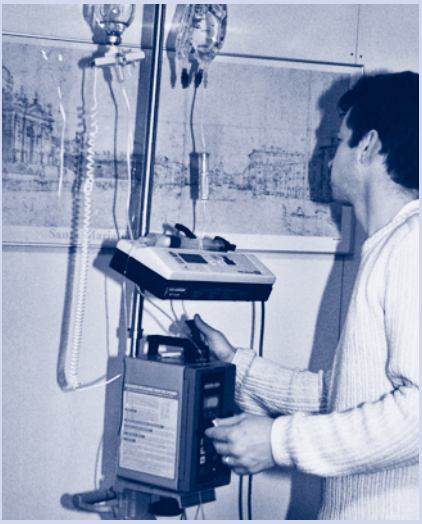
Chapter 6 A practical insulin infusion algorithm for the establishment of euglycaemia in both lean and obese patients with type 1 and type 2 diabetes



Alexander D.M. Stork, D. Willem Erkelens and Thiemo F. Veneman

Diabetes Res Clin Pract 2006;72:251-257.

Abstract

Background

Both in research and in various clinical situations, prolonged euglycaemia can be desirable. In recent years, its benefit in (critically) ill patients and patients with acute myocardial infarction has been established. The objective of this study was to assess safety and efficacy of a practical, bodyweight-dependent algorithm to establish euglycaemia in both lean and obese patients with type 1 and type 2 diabetes.

Methods

In 43 patients with type 1 diabetes, and 17 patients with type 2 diabetes insulin was infused overnight to establish euglycaemia. Plasma glucose concentration was determined at 45-minute intervals, and the insulin infusion rate was altered according to the algorithm.

Results

Baseline plasma glucose concentrations were 13.1 ± 4.4 and 12.7 ± 4.0 mmol/l in type 1 and type 2 diabetic patients, respectively. In both groups mean plasma glucose was reduced below 8.0 mmol/l within 3 hours, and averaged 7.4 ± 1.4 and 7.2 ± 1.0 mmol/l (P = 0.11) over the next 7 hours. Five (11.6%) patients with type 1 diabetes required administration of glucose because plasma glucose concentrations fell below 4.4 mmol/l. Consequently, type 1 diabetic patients were hypoglycaemic during 0.89% of the total study period. The lowest plasma glucose recorded was 3.9 mmol/l. In the type 2 diabetic patients the lowest plasma glucose was 5.5 mmol/l and no glucose administration was required for near-hypoglycaemia. The algorithm was equally effective in both lean and obese patients.

Conclusions

Euglycaemia was established simply, swiftly and safely during the study period with the practical weight-based algorithm used in this study, in both lean and obese type 1 and type 2 diabetic patients, with a very low rate of mild hypoglycaemia. The algorithm is applicable in research and various several clinical settings. Its validity for a prolonged period of time and in critically ill patients needs to be further evaluated.

Introduction

For various reasons, establishment and maintenance of euglycaemia during a prolonged period of time can be desirable. Overnight euglycaemia can be of use for initiation or adjustment of glucose lowering therapy, and to determine basal insulin requirements. Various research settings require euglycaemia. Moreover, in recent years evidence has become available of the importance of near-normoglycaemia in the (critically) ill. Van den Berghe et al. have clearly shown the benefits of maintaining euglycaemia in diabetic and non-diabetic patients in the intensive care unit. Morbidity as well as mortality was strongly reduced[1]. This was confirmed by Finney et al. in a prospective, observational study2. The Surviving Sepsis Campaign Management Guidelines Committee recommends maintenance of blood glucose levels in patients with severe sepsis below 8.3 mmol/l[3]. Finney et al. propose that the optimal glucose target is between 8.0 and 10.0 mmol/l[2]. Other studies have suggested that aggressive glucose control may improve clinical outcome in patients with acute myocardial infarction in coronary care units[4-6].

Several methods to induce and maintain euglycaemia have been developed. The hyperinsulinaemic glucose clamp technique is a frequently used and validated technique, but is very labor intensive[7]. In the past, closed loop insulin infusion systems (e.g. Biostator) have been used, but appeared not always successful nor reliable[8,9]. Automated closed-loop insulin infusion based on continuous glucose monitoring is potentially less labor intensive, but still experimental[10]. In addition, other open-loop insulin infusion systems in combination with various algorithms have been used in patients with diabetes[1,2,11-18].

To establish euglycaemia, we used a practical algorithm, adapted from a previously used algorithm by White et al.[11], which is simple to use and can easily be executed by nursing staff. This study includes a substantial number of lean and obese patients with type 1 and type 2 diabetes.

Methods

A total of 60 patients were studied: 43 patients with type 1 diabetes (age 39.2 ± 9.7 years [range: 20.9-70.8], body mass index 25.5 ± 3.5 kg/m^2 [range: 19.8-33.5], duration of diabetes 17.6 ± 8.9 years [range: 3-40], hemoglobin A_{1C} 8.1 ± 1.0 % [range: 5.7-10.3]), and 17 patients with type 2 diabetes (age 54.1 ± 12.8 years [range: 32.2-81.6], body mass index 28.5 ± 3.7 kg/m^2 [range: 22.4-37.6], duration of diabetes 7.8 ± 5.4 years [range: 2-21], HbA_{1C} 7.7 ± 1.6 % [range:5.6-12.0]). The establishment of nocturnal euglycaemia as described here, was performed in preparation of a glucose clamp the next morning. The study was approved by the institutional review board of the University Medical Center Utrecht, and all subjects gave written informed consent. All type 1 and type 2 diabetes patients treated with insulin were withdrawn from long and intermediate acting insulin for at least 24 hours before the study and managed with short acting insulin. The remaining type 2 diabetic patients were withdrawn from their oral

glucose lowering agents for at least 24 hours prior to the study. Patients were admitted to the University Medical Center Utrecht, Utrecht, the Netherlands at 2100 h. Around 2130 h two antecubital veins were cannulated for overnight infusion of insulin and blood sampling. The insulin infusate was prepared by adding regular insulin (Human Actrapid, Novo Nordisk, Gentofte, Denmark) to bags of normal saline, depending on the patient's weight, as shown in Table 1. All intravenous lines were primed before infusion was commenced. Intravenous infusion of insulin was started at 2200 h, by means of an IVAC infusion pump (IVAC 560, IVAC Corporation, San Diego, CA). Plasma glucose was determined at 45 minutes intervals (YSI 2300 STAT, Yellow Springs Instruments, Yellow Springs, OH). Infusion rates were adjusted by the unit nurse, according to the algorithm shown in Table 1. When a plasma glucose concentration was measured below 4.4 mmol/l, 10 ml of glucose 40% were given as a intravenous bolus, and plasma glucose concentration was measured again after 15 minutes. The algorithm was continued until 0800 h.

Table 1 Composition of the insulin infusate and the algorithm

Infusate composition	
Patient bodyweight (kg)	**Insulin concentration (U/l)***
60-65	80
65-70	88
70-75	96
75-80	104
80-85	112
85-90	124
90-95	140
>95	180
Infusion algorithm	
Plasma glucose concentration (mmol/l)	**Infusion rate (ml/h)**
< 5.5	0†
5.5-6.6	5
6.7-7.7	10
7.8-8.8	15
8.9-9.9	20
10.0-13.3	40
>13.3	60

* Insulin dissolved in saline
†If plasma glucose concentration is <4.4 mmol/l, administer 10 ml glucose 40% intravenously and measure plasma glucose concentration again after 15 minutes.

Data are given as mean ± SD and were evaluated with a two-sided 5% level of significance in Student's t-tests. To evaluate the algorithm's efficacy in both lean (body mass index < 25 kg/m^2) and obese (body mass index > 28 kg/m^2) patients, irrespective of type of diabetes, plasma glucose concentrations of 25 lean patients (body mass index 22.9 ± 1.4 kg/m^2 [range 19.8-24.9]) were compared to those of 17 obese patients

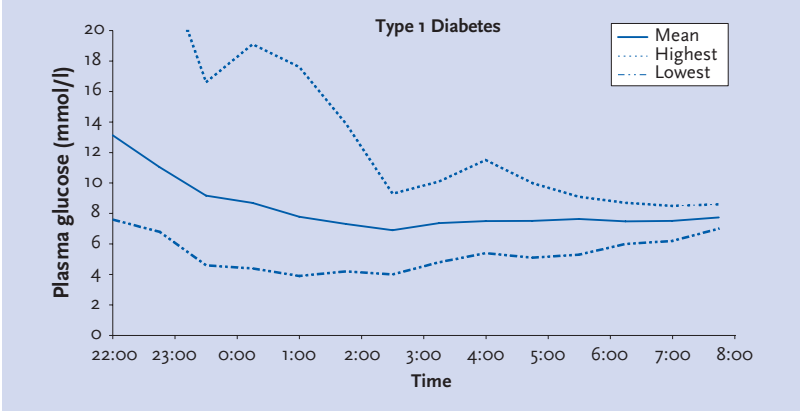
(body mass index 31.1 ± 2.7 kg/m^2 [range 28.1-37.6]). In addition, we wanted to determine whether insulin requirements were correlated with age, body mass index, hemoglobin A1C, initial plasma glucose concentration and duration of diabetes. For this purpose, data of the type 1 and type 2 diabetic patients were pooled and multiple linear regression analyses were performed with initial insulin requirement and total insulin requirement as respective dependent variables. Age, body mass index, hemoglobin A1C, initial plasma glucose concentration and duration of diabetes were independent variables.

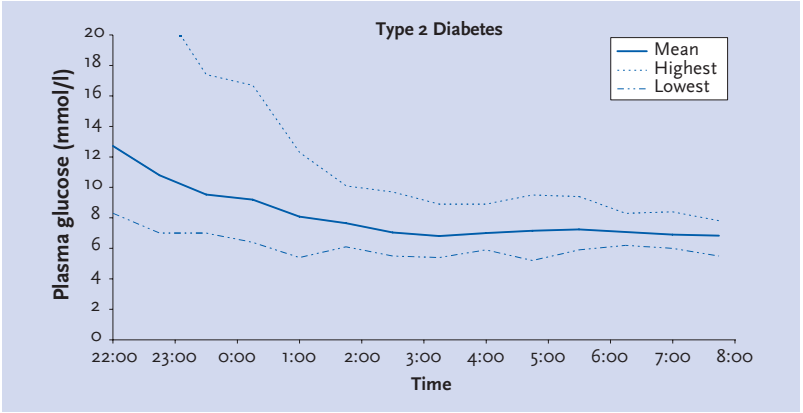
Results

Baseline plasma glucose concentrations were similar: 13.1 ± 4.3 and 12.7 ± 4.0 mmol/l in type 1 and type 2 diabetic patients, respectively (Figure 1.).
In type 1 diabetic patients, plasma glucose was reduced to below 8.0 mmol/l within 3 hours (2200-0100 h), and averaged 7.4 ± 1.4 mmol/l over the next 7 hours (0100-0800 h). During the last 4 hours (0400-0800 h), plasma glucose was maintained at a constant level of 7.5 ± 1.1 mmol/l with a coefficient of variation of 14.6%. The highest plasma glucose level between 0700 and 0800 h was 8.7 mmol/l, and the lowest was 6.0 mmol/l. The initial insulin infusion rate during the first 3 h required to reduce the plasma glucose concentration below 8 mmol/l was 2.2 ± 2.2 U/h (Figure 1). Subsequently, insulin requirements decreased, and over the last 4 hours averaged only 1.0 ± 0.7 U/h ($P < 0.0001$). Over the entire period, patients received 11.1 ± 5.8 U.
The dawn phenomenon was evidenced by an increase in plasma glucose concentration from 6.9 ± 1.3 at 0230 h to 7.6 ± 0.9 mmol/l at 0530 h ($P = 0.003$). This was accompanied by an increase in insulin requirements from 0.5 ± 0.6 U/h at 0230 h to 1.1 ± 0.7 U/h at 0530 h ($P < 0.0001$) (Figure 2). Over the entire period between 2200 and 0800 h only 5 patients (11.6%) required intravenous glucose injection (10 ml glucose 40 %) for plasma glucose concentrations below 4.4 mmol/l. Consequently, patients with type 1 diabetes were hypoglycaemic 0.89% of the total study period. Their plasma glucose concentrations at the time of glucose injections ranged between 3.9 and 4.3 mmol/l. No boluses were administered after 0230 h.

In type 2 diabetic patients, plasma glucose and insulin infusion rates followed a pattern similar to that observed in type 1 diabetic patients, with reduction to plasma glucose levels below 8 mmol/l after 3 hours, and an average of 7.1 ± 1.0 mmol/l over the next 7 hours. During the 4 last hours plasma glucose concentration averaged 7.1 ± 0.9 mmol/l with a coefficient of variation of 13.8%. These plasma glucose concentrations were slightly, although not statistically significantly, lower than those of the type 1 diabetic patients ($P = 0.11$). The highest plasma glucose level between 0700 and 0800 h was 8.4 mmol/l, and the lowest was 5.5 mmol/l. However, insulin requirements over the first 3 hours (5.6 ± 5.7 U/h), and insulin requirements over the last 4 hours (1.6 ± 1.4 U/h) were both significantly higher than those of the type 1 patients ($P < 0.0001$ and $P = 0.001$, respectively) (Figure 1).

Figure 1. Mean plasma glucose concentrations (mmol/l) during the study. Results of the type 1 diabetes patients in the upper panel, results of type 2 diabetes patients in the lower panel. The dotted lines indicate the highest and lowest values measured, respectively.





None of the type 2 patients required additional glucose injections for near-hypoglycaemia. A trend towards a dawn phenomenon, although not significant, probably because of the relatively small group size, was evidenced by an increase in plasma glucose from 6.8 ± 1.0 at 0230 h to 7.2 ± 1.0 mmol/l at 0530 h (P = 0.22) accompanied by a rise in insulin requirements from 1.3 ± 1.0 to 1.8 ± 1.3 U/h (P = 0.21) (FIGURE 2). Over the entire period type 2 patients received 25.2 ± 23.8 U, more than twice as much insulin as the type 1 diabetic patients (P < 0.0001).

When lean (body mass index < 25 kg/m^2) and obese (body mass index > 28 kg/m^2) subjects, irrespective of type of diabetes, were considered, there was no significant difference in plasma glucose concentrations at any point in time (P = 0.69 for all

values; FIGURE 3). Using multiple linear regression analyses, with initial insulin requirement and total insulin requirement as respective dependent variables, both body mass index and initial plasma glucose concentration were significantly correlated with initial insulin requirements ($P = 0.03$ and $P < 0.001$, respectively). Only body mass index was significantly correlated with final insulin requirements ($P < 0.01$).

Figure 2. Mean infusion rates (U/h) during the study. The solid line represents the type 1 diabetic patients, the dotted line represents the type 2 diabetic patients.

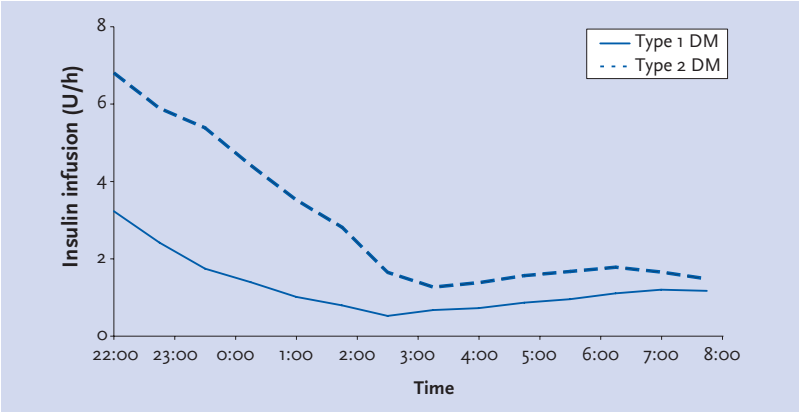
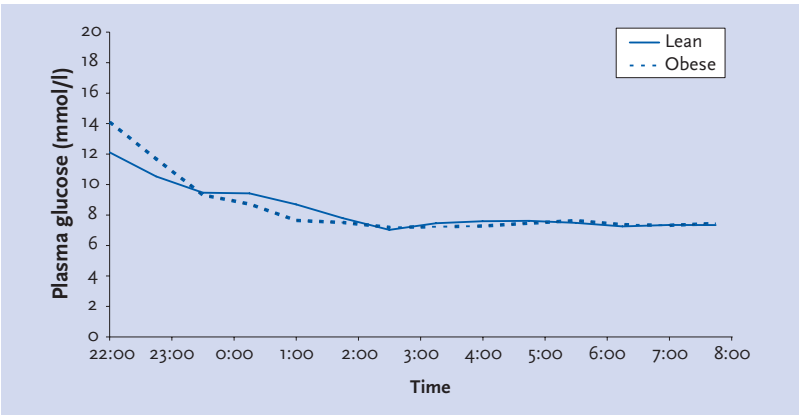


Figure 3. Mean plasma glucose concentrations (mmol/l) of lean (body mass index < 25 kg/m) versus obese (body mass index > 28 kg/m2) patients during the study, irrespective of type of diabetes. The solid line represents the lean patients, the dotted line represents the obese patients.



Discussion

We have demonstrated that the weight-based algorithm used in the current study is an effective and safe algorithm for establishing euglycaemia in both lean and obese patients with type 1 and type 2 diabetes.

After the initial stabilization phase, plasma glucose concentrations were maintained around 7.2 mmol/l. This is an adequate level for most clinical and research applications, e.g. determination of basal insulin requirement, or (re)institution of glucose lowering therapy. However, in the critically ill, Van den Berghe et al. have shown that the benefit of intensive insulin therapy was largest if blood glucose levels were below 6.1 mmol/l, which is equivalent to plasma glucose concentrations of <7.0 mmol/l[1], as glucose concentration in plasma is 10-15% higher than in whole blood[19,20]. Finney et al. suggest, based on their observational data, a target blood glucose level of less than 8.0 mmol/l (plasma glucose equivalent 9.2 mmol/l)[2]. Indeed, the Surviving Sepsis Campaign Management Guidelines Committee recommends maintenance of blood glucose levels in patients with severe sepsis below 8.3 mmol/l (plasma glucose equivalent 9.5 mmol/l)[3]. These targets are adequately met by the current algorithm. Should lower mean plasma glucose concentrations be desired, the algorithm could be modified towards more insulin infusion in response to glucose concentrations in the lower areas.

Theoretically, striving for lower plasma glucose concentrations will be accompanied by a higher rate of hypoglycaemia. This is evidenced by the study of Van den Berghe et al1. In their study target blood glucose levels were 4.4-6.1 mmol/l. In 5.2% of the patients who were intensively treated with insulin hypoglycaemia below 2.2 mmol/l occurred1. However, there were no serious complications, probably because these patients were continuously monitored on the ICU. In fact, most other studies reported a higher rate of hypoglycaemia[1,2,11-17] as compared to our results, including the study by White et al.11, from which the current algorithm was adapted and modified. They reported hypoglycaemia in 28% of the subjects, whereas in our study only 11.6% of the type 1 diabetic patients required glucose administration for plasma glucose concentrations below 4.4 mmol/l. In the study by Dazzi et al., an unconventional method was used, employing neural network software to apply fuzzy logic theoretical principles and to extrapolate rules, based on expert opinions, to a nomogram. Thus, a very effective algorithm was created, maintaining blood glucose concentrations at a mean of 7.8 mmol/l in critically ill patients. Nevertheless, 5.8% of the measurements were below 4.4 mmol/l[16]. Goldberg et al. reported that with the "Yale Insulin Infusion Protocol", 52% of the blood glucose concentrations were maintained between 5.5 and 7.8 mmol/l, and only 0.3% of the blood glucose levels were below 3.3 mmol/l. However, there were also three episodes of hypoglycaemia <2.2 mmol/l[18]. The percentage of time that our patients were hypoglycaemic was less than 1%, and the lowest plasma glucose concentration was 3.9 mmol/l. No glucose boluses were required after the first 4.5 hours of stabilization. Actually, none of our type 2 diabetic patients required glucose administration.

These differences may be largely explained by the frequent measurement of plasma

glucose concentrations in the current study: we measured at 45-minutes intervals, while most studies adapted 1-4 hours intervals. Furler et al. concluded from their computer simulation studies that an increase in sampling interval resulted in a decrease in blood glucose stability, and thus more frequent (and perhaps longer) hypoglycaemia. They suggest that a three-hour interval offers a good compromise between the degree of metabolic control and clinical effort[21]. Indeed, this seems more feasible if the algorithm is applied for a longer period of time e.g. during treatment on an ICU. Whether our algorithm would be as safe and efficacious when a longer interval of blood sampling and adjustment of the insulin infusion rate will be applied, remains to be determined.

From the mean baseline plasma glucose levels of approximately 13 mmol/l, with a wide range, euglycaemia was established within three hours. This period is comparable or slightly longer in studies in which similar algorithms were used[11,13,15]. The algorithm of Dazzi et al. was based on different principles and had a longer interval of plasma glucose measurement (four hours). Consequently, the time to establishment of euglycaemia was considerably longer (eight hours)[16]. With the algorithm of Goldberg et al.[18] euglycaemia was reached in a little over ten hours. In other studies in the critically ill, no data were presented on the rate at which euglycaemia was reached[1,2]. However, Van den Berghe et al. state that "normoglycaemia was safely reached within 24 hrs..."[22]. Accomplishing euglycaemia swiftly seems desirable in various clinical situations. Moreover, rapid establishment of euglycaemia could theoretically increase the benefit of intensive insulin therapy in critically ill patients, as the unfavorable period of hyperglycaemia is shortened in the course of the critical first 24 hours.

Our algorithm was designed to be very practical, and easy to use for the nursing staff. For reasons of practicality, in this study insulin was added to regular bags of saline and the intravenous lines were primed, but no serum albumin was added. It is a well known phenomenon that insulin can adsorb to intravenous delivery sets and glass or plastic containers[23,24]. Insulin delivery can be improved by priming the intravenous lines prior to the infusion[25-27]. Insulin adsorption can be reduced by adding serum albumin to the infusion solution, but this increases efforts and costs, and exposes the patients to human sera[28,29]. Although insulin delivery may have been influenced, particularly in the first hour of infusion[27], and perhaps euglycaemia could have been reached slightly faster, we do not feel that current results are largely affected.
Furthermore, the concentration of insulin in the infusate used in our algorithm is dependent upon the bodyweight of the patient, instead of a standard concentration independent of bodyweight as used in other studies. The weight-based composition of the infusate is important, since we wanted to accommodate lean type 1 diabetic patients as well as obese type 2 diabetic patients with the same uniform algorithm. It is also important because it ensures that rate adjustments are equal in all patients, which makes the algorithm easy to use. The body mass index of our patients varied between 19.8 and 37.6, and the algorithm was equally effective in lean as well as in obese patients.

The current study holds certain limitations. First, the results cannot automatically be transposed to critically ill patients, e.g. on intensive care or coronary care units. These patients may have, because of their critical condition, higher levels of catecholamines, cortisol and cytokines, leading to insulin resistance, and possibly hyperglycaemia. Therefore, maintenance of euglycaemia with the algorithm used in our study could be disturbed. Furthermore, catecholamine, cortisol and cytokine levels can alter as the condition of the patient improves or deteriorates, possibly leading to hypo- or hyperglycaemic disturbances. However, there was only a weak correlation between the Acute Physiology and Chronic Health Evaluation (APACHE)-II score, as an indicator of the condition of the patient, and insulin requirements22. Also, the results of the studies performed in critically ill patients, indicated that insulin requirements were subject to little change over the course of the illness[2,22]. The applicability of our algorithm in these patients therefore seems promising, but further research is needed to establish efficacy and safety in critically ill patients.
Second, the study period was limited to ten hours. No statement can be made on the algorithm beyond this period. However, as mentioned above, the variability in insulin requirement appears to be small, as also signified by the stability of the mean plasma glucose concentration and the tapered pattern of the highest and lowest concentration during the course of the study. Therefore, it seems likely that stable plasma glucose concentrations can be maintained beyond the study period.
Finally, it has to be pointed out that the glucose concentrations in the algorithm are measured and expressed in plasma, not whole blood. In clinical practice, glucose is typically measured bed-side in whole blood. As glucose concentration in plasma is 10-15% higher than in whole blood[19,20], the glucose concentrations in the algorithm should be converted to their whole blood equivalent when such a glucose meter is used.

In summary, the present study, including 60 both lean and obese patients with type 1 and type 2 diabetes, shows that euglycaemia is simply and swiftly established, and maintained during the study period using a practical weight-based algorithm in a safe and efficacious manner, with a very low rate of mild hypoglycaemia. It can be carried out by nursing staff using simple equipment, and may play an important role in a variety of research and clinical settings. Since severe hypoglycaemia did not occur, and the lowest plasma glucose concentration measured was 3.9 mmol/l, one could expect measurements at longer intervals to be safe. However, this remains to be proven. Also, this algorithm, although promising, needs to be further evaluated for its safety and efficacy for a prolonged period of time and in critically ill patients.

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This work is dedicated to the memory of D.Willem Erkelens (1941-2004).

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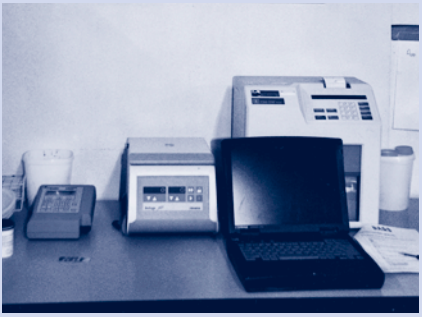
Chapter 7 Comparison of the accuracy of the HemoCue glucose analyzer to the YSI glucose oxidase analyzer, particularly in hypoglycemia



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Eur J Endocrinol 2005;153:275-281.

Abstract

Objective

We aimed to assess accuracy of the HemoCue, and correlation to the YSI 2300 STAT glucose oxidase analyzer, in particular for hypoglycemic values.

Research Design and Methods

Samples were taken from 24 volunteers during hyperinsulinemic glucose clamp studies. Glucose concentrations were determined immediately with the HemoCue in whole blood and with the YSI 2300 STAT in plasma from the same sample. After correction for the difference between whole blood and plasma, the paired plasma glucose concentrations were analyzed with various statistical methods.

Results

A total of 500 paired glucose values were obtained, 209 of which were in the hypoglycemic range. Mean values were 4.85 ± 0.004 mmol/l for HemoCue (range: 1.87-16.17) and 4.81 ± 0.004 mmol/l for YSI (range: 1.88–15.00; p=0.80). In the hypoglycemic region: 3.26 ± 0.004 mmol/l for HemoCue (range: 1.87-5.17) and 3.22 ± 0.003 mmol/l for YSI (range: 1.88–4.20; p=0.59). Regression analysis: HemoCue=1.019(YSI) - 0.0577 mmol/l, with r=0.9787 for all values; for hypoglycemic values: HemoCue=1.1169(YSI) - 0.3393 mmol/l, with r=0.8798. Altman's residual plot: difference was 0.03 ± 0.0009 mmol/l, with 18 (3.6%) paired values outside 95% limits of agreement (-0.82–0.89 mmol/l). In the hypoglycemic range difference was 0.04 ± 0.001 mmol/l, with six (2.9%) values outside 95% limits of agreement (-0.71–0.79 mmol/l). Error grid analysis: one value was in Zone D (0.2%), and five values (1%) were in Zone B. 98.8% Were within Zone A.

Conclusions

Determination of glucose with the HemoCue system has very good correlation to the YSI in a broad range of glycemia, also for hypoglycemic values. We believe that these methods can be used interchangeably for research and clinical purposes in adults.

Introduction

The incidence and prevalence of type 1 and type 2 diabetes mellitus is increasing throughout the world. Recently new diagnostic criteria have been established by the American Diabetes Association, depending on glucose measurements after an overnight fast and after oral glucose loading (OGTT)[1]. Because identification of diabetic patients and early treatment is important, ideally, these measurements should be performed in the doctor's office, with high accuracy and results rapidly available. Moreover, it has recently been established that aggressive glucose control improves clinical outcome in critically ill patients on intensive care and coronary care units[2-4]. Also, a growing amount of research is performed in the field of diabetes, both in the laboratory and in the field. Therefore, there is an increasing need for an accurate, swift and easy to operate method of glucose determination. Most currently marketed hand-held devices for home glucose determination do not offer sufficient accuracy and precision, especially in the hypoglycemic region, where accurate determination of glucose can be crucial for diagnosis and treatment[5-15].

There is no universal agreement on a reference method for glucose determination[16-19]. The hexokinase method is frequently used as reference method in laboratory settings. The glucose oxidase method is frequently used and generally accepted as standard method when swift glucose readings are required, e.g. during glucose clamps. Although quick and proven sufficiently accurate in a large range of glycemia, including low values, there are certain disadvantages to the glucose oxidase method, as employed for example in the Yellow Springs Instruments 2300 STAT (YSI). The analyzers are relatively large, non-portable, interference and technical malfunction can easily occur, they require careful maintenance, and can only be operated by trained technicians. HemoCue is an instrument that uses a dual wavelength photometer to measure glucose in hemolyzed whole blood after a modified glucose dehydrogenase reaction. Because it's portable, it can be used pre-analytically and bedside. It requires very little maintenance, operation is simple, and technical malfunction rarely occurs. In previous research the accuracy of the HemoCue system has been compared to several reference methods[5-7,20-36]. In some studies accuracy compared well[20-29], whereas in other studies considerable differences were found between HemoCue measurements and the reference method[5-7,30-36]. However, several confounding factors could have played a role in the variable results.

We aimed to assess accuracy of the HemoCue, and correlation to the YSI, in particular for hypoglycemic glucose values, using various statistical methods, and correcting for potential biases.

Methods

Samples were taken from 24 volunteers (14 male, 10 female, mean age 43.8 years, range 29.3 to 67.4), participating in a hyperinsulinemic glucose clamp study that was performed for other purposes. None of the subjects had triglyceride levels >3 mmol/l or used ascorbic acid. Average hematocrit was 0.43 (range 0.38 to 0.51).
During the hyperinsulinemic glucose clamp studies, two antecubital veins were cannulated. Via one cannula insulin and glucose were infused. Blood samples from the second cannula in the other arm were arterialized, using a heating sleeve to warm the arm to 55 °C. When withdrawing blood, the first two milliliters were discarded, and immediately thereafter a sample of approximately one milliliter was drawn for analysis. From this sample, a small amount was placed on a sample glass for immediate analysis with a HemoCue ,-Glucose system (HemoCue AB, Angelholm, Sweden). As plasma glucose concentrations were required for the clamp studies, the remainder of the blood sample was put into a vial and immediately centrifuged for 15 seconds at 5,800 G. Subsequently, the glucose level in plasma was analyzed with a glucose oxidase method (YSI 2300 STAT, Yellow Springs Instruments, Yellow Springs, OH, USA).
Both instruments were maintained according to the manufacturers' recommendations. Additionally, the YSI was calibrated at the start of every day and after every five samples or a maximum of half an hour, whereas the calibration of the HemoCue was checked before every session with the manufacturer's control cuvette. Also, the HemoCue's microcuvettes were stored and handled according to the manufacturer's recommendations.

Statistical analysis

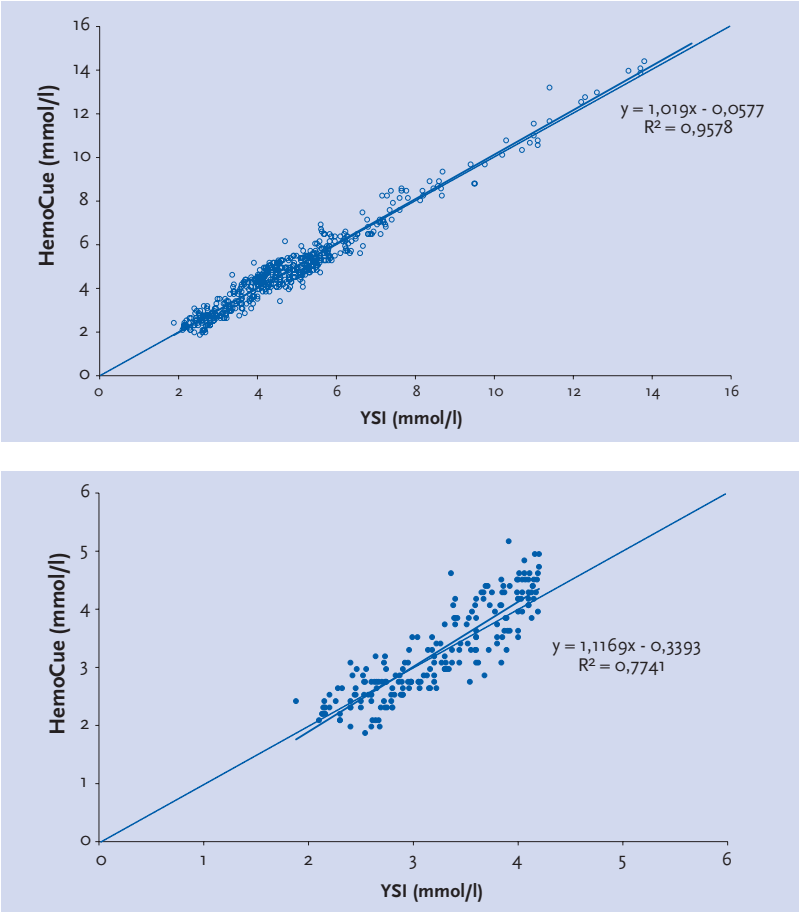
Mean values were calculated and regression analysis was performed. Subsequently, before further analysis, the HemoCue results were corrected for the difference in glucose concentration between whole blood and plasma (HemoCue plasma=1.10 (HemoCue whole blood)). Plasma glucose concentrations of <4.2 mmol/l on the reference method were considered hypoglycemic, in accordance to the guidelines for blood glucose monitoring systems of the International Organization for Standardization (ISO)[37]. This does not necessarily correlate with clinical hypoglycemia. Several different statistical methods were applied to these paired plasma glucose values, analyzing all paired values, as well as the hypoglycemic values separately (plasma glucose on YSI <4.2 mmol/l): *a)* Mean values *b)* Regression analysis *c)* Two-tailed Student's T-test on mean values of HemoCue and YSI with levels of significance defined as $p<0.05$. *d)* Percentage of HemoCue values within 5, 10, 15, 20, and 30% and within 0.2, 0.5, 0.83, 1.0 and 1.5 mmol/l of the YSI value, respectively. *e)* Difference between the HemoCue value and the YSI value plotted against the average of the paired values, according to Altman´s residuals method[38]. *f)* Error grid analysis[15].
Data are presented as mean ± SE, unless otherwise indicated.

Results

A total of 500 paired glucose values were obtained, 209 of which were considered hypoglycemic (plasma glucose on YSI <4.2 mmol/l).

Mean HemoCue whole blood glucose was 4.41 ± 0.004 mmol/l (range 1.7-14.7), mean YSI plasma glucose was 4.81 ± 0.004 mmol/l (range: 1.88 to 15.00; p=0.001).

Figure 1 Regression line and regression equation (after 10% correction for the difference between whole blood and plasma glucose concentration) for all values in the upper panel (open dots) In the lower panel for hypoglycemic values separately (YSI<4.2 mmol/l; solid dots).



For the hypoglycemic samples, mean HemoCue whole blood glucose was 2.96 ± 0.003 mmol/l (range: 1.7 to 4.7), mean YSI plasma glucose was 3.22 ± 0.003 mmol/l for YSI (range: 1.88 to 4.20; p<0.0001). Regression analysis showed the following relationship: HemoCue whole blood=0.9264(YSI) - 0.0525 mmol/l, with r=0.9787.

After correcting the HemoCue values for the difference between whole blood and plasma glucose concentration, there was no significant difference between the mean values of HemoCue and YSI plasma glucose concentration (4.85 ± 0.004 vs. 4.81 ± 0.004 mmol/l; p=0.80). The relationship with regression analysis between these values was HemoCue=1.019(YSI) - 0.0577 mmol/l, with r=0.9787 (Figure 1). In the hypoglycemic region mean value after correction was 3.26 ± 0.004 mmol/l for HemoCue (versus 3.22 ± 0.003 mmol/l for YSI; (p=0.59)). Regression analysis for the hypoglycemic region yielded HemoCue=1.1169(YSI) - 0.3393 mmol/l, with r=0.8798 (Figure 1). The paired plasma glucose values after 10% correction of the HemoCue whole blood results to HemoCue plasma glucose results were used for further analysis.

The percentage of HemoCue plasma values within relative and absolute margins of the paired YSI values are shown in Table 1. As expected, when all values were considered, there were significantly higher percentages within the relative margins mentioned than when only hypoglycemic values were considered. However, there were no significant differences in the percentages of values within the absolute margins, although there was a trend towards higher percentages of hypoglycemic values within the absolute margins.

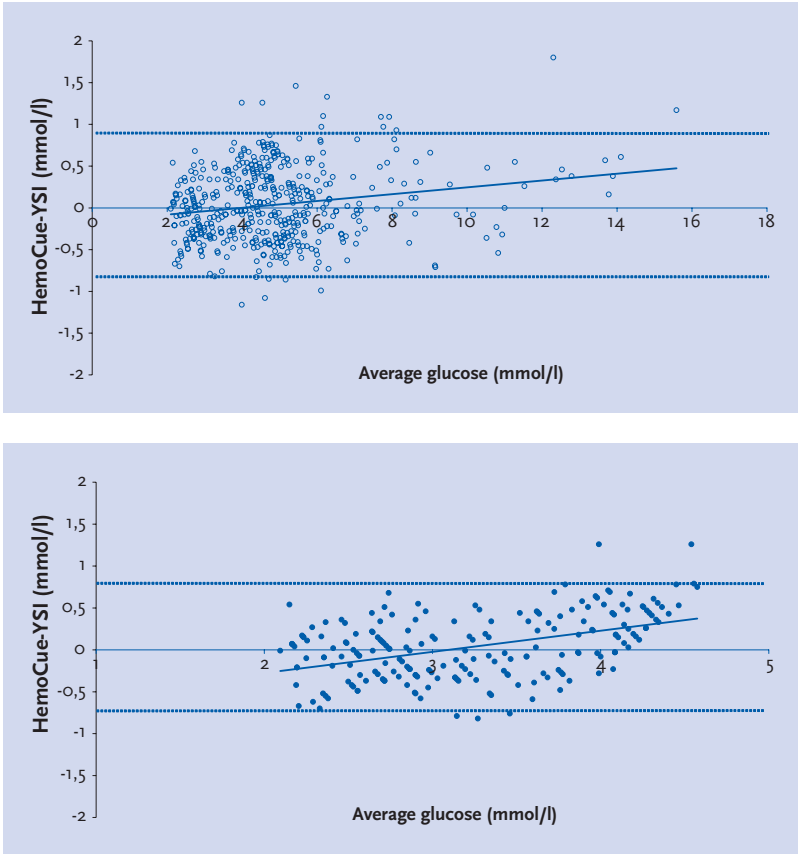
Table 1 Percentage of HemoCue plasma values within margins of YSI value

Margin	Hypoglycaemic values (%)	All values (%)	P
Relative			
± 5%	29.2	37.8	0.029
± 10%	56.9	67.4	0.0079
± 15%	79.9	87.4	0.01
± 20%	92.8	96.0	0.075
± 30%	99.0	99.4	0.61
Absolute			
± 0.2 mmol/l	35.9	32.2	0.34
± 0.5 mmol/l	79.9	75.0	0.16
± 0.83 mmol/l	99.0	96.4	0.053
± 1.0 mmol/l	99.0	97.8	0.26
± 1.5 mmol/l	100	99.8	0.51

The plot of the individual differences between YSI and HemoCue against the average of the two measurements showed a difference of 0.03 ± 0.0009 mmol/l. For 18 (3.6%) paired values the difference was outside the 95% limits of agreement (-0.82 to 0.89 mmol/l). Plotting the individual differences in the hypoglycemic range showed a

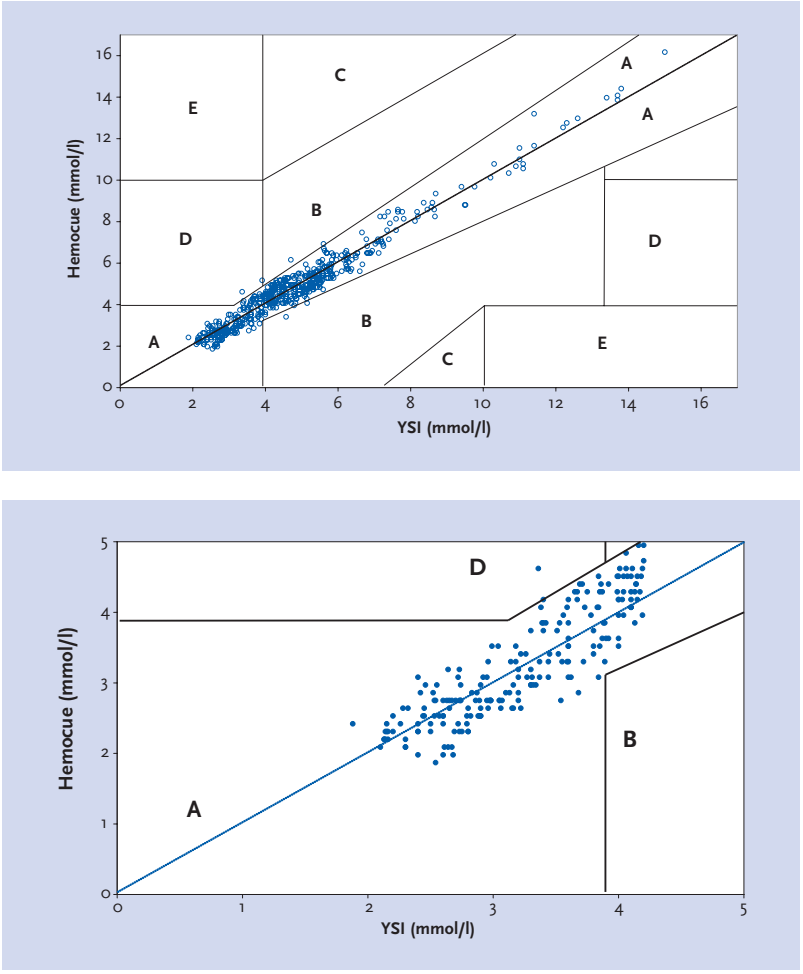
difference of 0.04 ± 0.001 mmol/l. Six (2.9%) were outside the 95% limits of agreement (-0.71 to 0.79 mmol/l) (FIGURE 2).
When using error grid analysis with YSI-values as reference method, all hypoglycemic HemoCue values except 1 (99.5%) were within the clinically accurate Zone A. 1.4% of the values were in Zone D, possibly leading to dangerous failure to detect and treat. When plotting all values on the error grid, the same one value was in Zone D (0.2%),

Figure 2 Altman's residual plot (mean of paired values plotted against the absolute difference between paired values), with 95% limits of agreement (mean ± 1,96 SD; broken lines) and regression line. In the upper panel Altman's residual plot of all values (open dots). For 18 (3.6%) paired values the difference was outside the 95% limits of agreement (-0.82 to 0.89 mmol/l). In the lower panel the plot of the hypoglycemic values separately (YSI<4,2 mmol/l; solid dots). Six (2.9%) were outside the 95% limits of agreement (-0.71 to 0.79 mmol/l).



and five values (1%) were in Zone B, the zone with benign estimate errors. Of all HemoCue values 98.8% were within Zone A (FIGURE 3).

Figure 3 Error grid analysis of the HemoCue plasma glucose concentrations (Y-axis) with the YSI as reference method (x-axis). All values are plotted in the upper panel (open dots); 98.8% were within the clinically accurate Zone A. One value was in Zone D (0.2%), possibly leading to dangerous failure to detect and treat, and five values (1%) were in Zone B, the zone with benign estimate errors. Error grid analysis for the hypoglycemic values separately (YSI<4.2 mmol/l; solid dots) are plotted in the lower panel. All hypoglycemic HemoCue values except 1 (99.5%) were within Zone A. 1.4% of the values were in Zone D.



Discussion

To our knowledge, this is the largest series of paired glucose determinations with the HemoCue system described in literature, especially for hypoglycemic values. The YSI glucose analyzer, a glucose oxidase system, is currently most frequently used when direct and accurate determination of glucose concentration is needed, but carries disadvantages in certain situations. Therefore, we have compared accuracy of the HemoCue β-Glucose system to the frequently used and well established YSI 2300 STAT. The HemoCue measures glucose in whole blood after hemolysis, rather than in plasma. However, in research and in most clinical guidelines, generally plasma glucose concentrations are described. As glucose concentration in plasma is approximately 10-15% higher than in whole blood, depending on hematocrit and on the method of whole blood analysis[39,40], we applied a conversion factor (1.10) to the paired values before further analysis. This resulted in mean values that were very similar, and not statistically significantly different, and in a regression slope very close to 1. Naturally, the correction had no effect on correlation (r=0.9787). Our finding that correlation was higher in the whole range (1.9 to 15.0 mmol/l) than in the hypoglycemic range (1.9 to 4.2 mmol/l) was not surprising, as relative margins increase at lower glucose levels, and the coefficient of variation is higher in the lower range of virtually every laboratory test. This effect was enhanced by the fact that the HemoCue displays the result in only 1 decimal, whereas the YSI displays 3 decimals. It is of note that the relationship between the two methods appeared not to be uniform across the whole range of glucose concentrations. In the lower range agreement was very close, but for values over 8 mmol/l and particularly over 11 mmol/l there was a tendency towards higher results of the HemoCue at higher concentrations. Indeed, in some previous studies this trend can also be observed[5,22,30], although not clearly present in other studies[13,24]. Because the number of measurements is relatively small, implications are unclear.

We found very small absolute differences between mean values of HemoCue and YSI, both for all values, in a range from 1.9 to 15.0 mmol/l, and in the hypoglycemic range, which were not statistically significant. However, one has to be aware of the relatively low discriminative power of this test. A more discriminative method of comparison is plotting the differences between the standard method and the test method against the average of the two measurements, according to Altman´s residual method[38]. In the current study, approximately 97% of all paired measurements are within the 95% limits of agreement, also when hypoglycemic values are considered separately. Therefore, the two methods considered in this study agree sufficiently to be used interchangeably[41]. Considering these data, one also has to bear in mind that there is no universally agreed reference methodology for blood glucose measurement. All methods used in clinical laboratories and in research show some inaccuracy and variation when compared to each other or to isotope dilution-mass spectrometry[17,29].

The criteria recommended by the American Diabetes Association (ADA) for home blood glucose measuring devices, stating that all glucose results of a device should be

within 5% of the reference values[42], are not met. Considering the discussion on reference values mentioned above, these criteria are very stringent. The International Organization for Standardization (ISO) is more lenient. They propose that 95% of measurements should be within ±20% of the reference method, or within 0.83 mmol/l for values <4.2 mmol/l[37]. In this study the ISO-criteria, with YSI as reference method, are amply met (98.3 and 99.0%, respectively). Recommended criteria of both organizations, however, are concerning home blood glucose measurements, not laboratory devices.

Error grid analysis was developed by the research group of Cox and Clarke, to determine clinical accuracy of glucose results, taking into account both the difference between the reference and the test method values, and the pertinence of the treatment decision resulting from the test method value[15,43]. According to this analysis, only a single HemoCue measurement (0.2%) could potentially have led to a dangerous failure to detect and treat hypoglycemia, and five (1.0%) measurements could have resulted in benign estimation errors. All other measurements (98.8%) are clinically acceptable. Taking into account the large sample size, these results are clinically very satisfactory.

As mentioned in the introduction, there has been discussion in literature on the accuracy of the HemoCue blood glucose measuring device[5-7,20-36]. Several confounding factors could have played a role in the variable results. Sample handling and preservation could have biased results of certain studies, as samples for HemoCue and for the reference method were handled differently. Determination of glucose concentration at different times after drawl of blood allows for pre-analytical glucose usage by cells, even when the blood is stored in sodiumfluoride, as this does not completely inhibit glycolysis, particularly in the first hours[44]. Moreover, several studies compared results from capillary blood to those of venous blood or plasma; these concentrations can differ considerably, especially in the postprandial state[45]. Also, in some studies the authors did not correct the HemoCue results in whole blood to plasma values. Furthermore, a number of, primarily early, studies used statistical methods with low discriminatory power (e.g. regression analysis, Coefficient of Variation). In nearly all of the studies, there was a low number of hypoglycemic samples. This has been further complicated by the fact that the device has been studied a number of times for neonatal hypoglycemic samples, which is a very specific patient group, different from adults in several ways. Although one study[46] showed no marked effect of hematocrit on glucose measurements presumably, although not mentioned specifically, in adult blood, it is possible that either hematocrit or other factors in neonatal blood have influenced results[47]. When discussing the data provided by studies on blood glucose measurement, we believe that the accuracy and variability of the reference method used should also be taken into account, as there is no generally accepted gold standard, except perhaps for isotope dilution-mass spectrometry. Therefore, a discrepancy between two paired measurements of two devices does not necessarily implicate that the tested method is inferior to the reference method used.

In the current study we have used the YSI as reference method, as it is a frequently used and well established analyzer for immediate and accurate glucose determination in research and clinical applications. On the other hand, it has certain disadvantages, not carried by the HemoCue. We have tried to diminish confounding factors such as type of blood (capillary versus venous), storage of the samples, delay of measurement, and conversion to plasma glucose values. Values in the hypoglycemic region, where inaccuracy is most likely to occur, and can potentially lead to dangerous clinical situations, were considered specifically. Also, various methods of analysis with lower and higher discriminatory power have been used, aiming for assessment of accuracy, and in particular to determine how HemoCue compares to the YSI. This study meets limitations in its focus on accuracy proper of the HemoCue. It does not describe correlation between venous glucose concentration as determined by a reference method (or the HemoCue) and capillary glucose concentration measured with the HemoCue. Furthermore, the samples analyzed were from adults with hematocrits within a range of 0.38 to 0.51. The results cannot be transposed automatically to determinations in samples with higher (or lower) hematocrits or from neonates.

The results of this study show that determination of glucose with the HemoCue system has very high correlation to measurement with the YSI in a broad range of glycemia, and in hypoglycemia in particular. We believe that these methods can be used interchangeably for research and clinical purposes in adults. However, the criteria of the ADA for blood glucose measuring devices were not met. It must be noted that, for reasons discussed, no statements can be made on accuracy in neonates.

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This work is dedicated to the memory of D.Willem Erkelens (1941-2004).

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Chapter 8 Diabetes and the driving license

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Introduction

In the Netherlands, as in many other countries, a driving license is required to be allowed to participate in motorised traffic. The public body which is authorised to issue these driving licenses, has to issue the driving license to the driver for the specific type of vehicle he is allowed to drive (article 107 of the Dutch Road Traffic Act (WVW) 1994[1]). A driving license is only issued to those drivers who possess sufficient driving ability and fitness (article 111 section 1 under b of WVW 1994).
By demanding sufficient driving ability (does the driver know the traffic rules and does he master the vehicle?) and fitness (does the driver possess sufficient *physical and mental* fitness to enable him to participate in road traffic?) the legislator intends to maintain the risk of road traffic accidents within reasonable boundaries. A certain risk of road traffic accidents has to be accepted: only the total absence of traffic can guarantee a 100% safety level in traffic. One of the problems in determining the acceptable boundaries of the risk of road traffic accidents the legislator is confronted with, is the circumstance that the relationship between health conditions and the risk of road traffic accidents is often difficult to measure.
Some diseases and disorders, e.g. blindness or serious mental illness, represent an evident inability to participate in motorised road traffic. Of various other disorders, however, it is assumed that they can negatively influence the driving ability under circumstances. Examples are epilepsy, various eye diseases, severe lung disease, et cetera. Also patients suffering from diabetes mellitus (hereinafter: "diabetes") can be subject to hazardous road traffic situations because of their illness, causing a higher risk of road traffic accidents and therefore less driving ability.

In this article we intend to elaborate on the theory and praxis of the current legislation regarding diabetes, to point out the bottlenecks and to discuss the question, whether the demands set in the current legislation for diabetics participating in motorised road traffic need amendment.

[1] In Dutch: Wegenverkeerswet 1994, hereinafter to be referred to with its Dutch acronym: "WVW 1994".

About diabetes

For a proper understanding of current legislation concerning diabetes and driving, some explanation of the disease is essential.

Disease and incidence

Diabetes is a disorder which is becoming ever more frequent among the populations of both Western and Non-Western countries. Diabetes is characterised by an absolute (type 1, the so-called "auto-immune diabetes") or a relative (type 2, "old people's diabetes") shortage of the hormone insulin. This hormone is normally produced in the pancreas, and is required for the transport of glucose from the blood current to the tissues, where the glucose can be utilised as fuel for the body cells. At the moment, in the Netherlands, an estimated amount of 40,000 people suffer from type 1 diabetes and approximately 400,000 people suffer from type 2 diabetes.
Because of the shortage of insulin, the blood glucose concentration rises in patients with diabetes, whereas in the healthy body the glucose concentration only varies within very narrow boundaries.
Without adequate medical treatment both type 1 and type 2 diabetes cause serious health problems. The treatment of type 1 diabetes always consists of subcutaneous insulin injections. Type 2 diabetes may be treated with tablets, which either stimulate the production of insulin by the pancreas, or make the body cells more susceptible to the body's own insulin. However, often additional treatment with subcutaneous insulin injections is required, particularly in prolonged disease.

Hyperglycaemia and hypoglycaemia

Even with modern treatment it is impossible to keep the blood glucose concentration within the normal, aforementioned narrow, boundaries at all times. It is therefore inevitable that regularly glucose concentrations occur, which are well above or below the normal values. These values are called hyperglycaemia or hypoglycaemia, respectively. Hyperglycaemia will only seldom, in extreme cases, lead to acute illness and cognitive function loss, relevant for the participation in road traffic.
In the case of hypoglycaemia, however, an acute shortage of glucose in the brain cells occurs. Contrary to other body cells, brain cells cannot switch to an alternative fuel, e.g. fat, to ensure energy supply. The brain functions will therefore inevitably decrease because of the shortage of glucose, causing cognitive dysfunction (the patient "goes at sea").
Furthermore, under the influence of diabetes, chronic complications of the kidneys, eyes, nerves and blood vessels can develop in the long run. Because these physical complications can also be found in people who do not suffer from diabetes, and because principally acute hypoglycaemia, causing the patient to suddenly "fall out", is considered the greatest threat to the safety of diabetic patients in road traffic, the chronic complications of diabetes are left out of account in this article.

A closer look at hypoglycaemia

The occurrence of a low glucose concentration in the blood (hypoglycaemia) constitutes the largest threat to the driving ability of the diabetic driver.

The glucose concentration in the blood can decrease pursuant to three causes:
- too little food;
- too large a physical effort (causing the body to use up glucose) or
- too high an insulin level, causing the glucose present in the blood to be transferred too quickly into the cells.

Too high an insulin level is caused when more insulin gets into the blood than the body needs at a certain time. This can either arise from using insulin or from taking tablets which stimulate the pancreas to produce more insulin. Medication that makes the body cells more susceptible to the body's own insulin, generally does not cause hypoglycaemia.

If the blood glucose concentration is too low, usually the classical symptoms of hypoglycaemia occur: sweating, distress, trembling, palpitations, cold hands and hunger. These symptoms serve to warn the patient to consume carbohydrates (by eating or drinking something sweet) in order to restore the normal glucose concentration. If the patient fails to do so, at a certain point in time the brain function will decline. Confusion, dizziness, reduced eyesight, and a decrease of the ability to think and concentrate will consequently occur.

These consequences will grow more serious as the glucose concentration further decreases and therefore the brain cells receive less fuel. Without proper treatment the glucose shortage will lead to unconsciousness, coma and, eventually, death. If the person has to rely on others to restore the normal glucose concentration and as a result allow the brain to function normally, or if the patient loses consciousness, this is called severe hypoglycaemia.

Perception of hypoglycaemia: impaired awareness and unawareness

The typical order of symptoms and course of the decreasing blood glucose level are described supra. The perception of hypoglycaemia, however, varies per patient and can also be subject to change in the course of the disorder.

In patients who regularly suffer from hypoglycaemia, the warning symptoms may occur at a increasingly lower glucose concentration in the blood, so that the period between the occurrence of symptoms and the decrease of brain functions, may be so short that the patient cannot adequately respond to the symptoms himself. In some cases brain functions even decrease before warning symptoms occur.

The phenomenon that diabetic patients do not notice warning symptoms of a decreasing glucose level until at a late stage of hypoglycaemia is called *impaired* hypoglycaemia awareness; if the diabetic does not notice the warning symptoms at all, this is called hypoglycaemia *unawareness*.

Impaired hypoglycaemia awareness and hypoglycaemia unawareness are conditions which can easily convert into one another. A single episode of hypoglycaemia may bring about impaired hypoglycaemia awareness. In its turn, because of the fact that the symptoms occur at a later stage or do not occur at all before brain functions are decreased, impaired hypoglycaemia awareness in itself increases the chance of a new severe hypoglycaemia, further reducing awareness. Consequently, a vicious circle of decreasing awareness and increasing risk of more severe hypoglycaemias arises. Conversely, the avoidance of hypoglycaemias for a longer period of time, may increase

the period between the warning symptoms and the decrease of the brain functions (again).
Pursuant to an number of scientific studies, the trend in the last couple of years has been to strive to bring the glucose level of diabetic patients as close to normal levels as possible. Resulting from this, the risk of hypoglycaemia increases, since, because of the narrow margins, a relatively small shift of the blood glucose concentration can cause the glucose concentration to decrease below normal levels. This in turn leads to a higher frequency of impaired hypoglycaemia awareness. Currently approximately 25% of patients with type 1 diabetes suffer from hypoglycaemia unawareness. Due to various medical aspects, this percentage is approximately ten times lower in type 2 diabetes.

The Fitness Criteria Regulations 2000

The criteria with regard to physical and mental fitness to drive motorised vehicles have been regulated in the Annex of the Fitness Criteria Regulations 2000, which were lastly amended in June 2004 (hereinafter: "the Annex")[2]. See also Appendix A.
The Annex consists of ten chapters, in which the Minister of Transport, Public Works and Water Management has formulated criteria to assess the physical and mental fitness to drive a motorised vehicle. The Minister has been given advise by the Health Council in formulating these criteria.
Generally, the criteria set in the Annex are more flexible for group 1 driving licenses (motorcycle, private car) than for group 2 driving licenses (lorry, coach). This article will only discuss the group 1 driving licenses: motorcycles and private cars.
Diabetes has been listed in chapter 5 of the Annex (internal diseases) as one of the disease for which specific criteria have been formulated. Current criteria are based on a report published by the Health Council in 2002[3].

[2] Stcrt. 2000,99; amendments in Stcrt. 2000,20; Stcrt. 2004, 50; Stcrt. 2004, 106.

[3] Health Council. [Fitness to drive in persons with diabetes mellitus.] The Hague, the Netherlands: Health Council, 2002.

Diabetes and the driving license

The Driver's Declaration Procedure

The assessment of driving ability is delegated to the civil law foundation Central Vehicle Licensing Agency (hereinafter: CBR). If the driving ability has been established, the CBR issues the so called Declaration of driving ability (articles 97-104 of the Driving Licenses Regulations). This declaration is requested by the (aspirant)driver by sending a medical questionnaire, the so called "Driver's Declaration" form which is to be filled out and signed by the applicant himself. The Driver's Declaration consists of 11 questions about diseases and (functional) disorders which are relevant for the assessment of the driving ability and from which the applicant might suffer. If one of the questions of the Driver's Declaration has been answered by "yes", a physician has to indicate the nature and the severity of the disorder in the Driver's Declaration. The Rules of Conduct of the physicians' organisation KNMG still stipulate that the physician in question should not be the physician who treats the patient[4], although the road traffic legislation does not forbid this.

If the applicant is 70 years of age or older, the physician also has to fill out the Medical Report which is an annex to the Driver's Declaration after performing a minor medical examination.

A person with type 1 or type 2 diabetes has to answer question 5 of the questionnaire *"Are you being treated or have you been treated for (...) diabetes (...)?"* by *"yes"*.

Group 1 driving licenses only require a medical report by a physician in the Driver's Declaration, stating the nature and severity of the disorder (Driver's Declaration form, note 1). Based on this information, the CBR can decide that further examination by a (medical) specialist is desirable. This specialist advises the CBR about the driving ability and the duration of the driving license which may be issued. Based on the available information and reports of medical specialists, if present, the CBR decides whether a Declaration of fitness based on the criteria in the Annex can be issued, or further examination is necessary, e.g. by performing a driving test in the presence of a CBR expert.

The Demand Procedure

Beside the Driver's Declaration procedure, the CBR also has another procedure to assess the driving ability of the driver: the so called Demand Procedure (articles 130-134 WVW 1994).

In the Demand Procedure the Demand Division of the CBR demands that the holder of the driving license who is suspected to be unfit to drive a motorised vehicle, be examined. This is not a voluntary examination; the CBR sanctions the refusal to participate by declaring the driving license invalid. The General Director of the CBR and the police are authorised to inform the Demand Division of the suspicion of unfitness to drive a motorised vehicle.

The police can give the information based on its own perception. The grounds on

[4] Communication of the Secretary of the KNMG, ["No medical examinations for the driving license by own General Practitioner", Medisch Contact 1997, 25.5

which the police may base its information are stipulated in the Measures Driving Ability and Fitness Regulations[5].
The most common reason for the police to give information is driving under influence of alcohol, suspecting alcohol abuse. However, a black out behind the wheel (e.g. because of hypoglycaemia) or functional disorders of the limbs (e.g. because of nerve damage) may also be a reason to inform the Demand Division of CBR. The Demand Division of CBR assesses the information and determines which examination has to take place.
The General Director of the CBR is authorised to inform about the suspicion of unfitness based on written information of reliable third parties received by him. The reliable third party can be the physician treating a patient for a serious medical problem, who will not give up driving voluntarily. A physician's notification, however, is a breach of the duty of confidentiality of the physician, stipulated in article 7:457 Dutch Civil Code, which is only admissible if legislation obliges the physician to do so (which is the case with some infectious diseases), or if the interest to breach of the duty of confidentiality outweighs the interest stipulated in article 7:457 Dutch Civil Code. This interest serves to prevent the ill to refrain from consulting a physician for fear that the physician treating the patient might make the information public. (Cf. Judgment of the Supreme Court of the Netherlands, April 20, 2001, RvdW 2001, 87).
In 2003, physicians indicated to the CBR 28 times that a patient might be seriously less fit to drive a motorised vehicle. In 2004, 24 reports were filed[6].

Period of validity

By virtue of section 5.2 of the Annex, persons with diabetes only qualify for driving licenses of a limited period of validity. For group 1 driving licenses, the period of validity has a maximum of 10 years.
Specific criteria for obtaining a driving license are stipulated in the Annex for people who use insulin or other medicine which can cause hypoglycaemia. They have to be free from chronic complications, to be able to anticipate hypoglycaemias and to adequately deal with hypoglycaemias, and to be regularly checked by a diabetes specialist. The physician's report in the Driver's Declaration has to reflect on the aforementioned criteria. Every ten years a report by an ophthalmologist is required.
Persons who use medication that does not generally cause hypoglycaemias only need to be free from the complications. Similarly, based of the report of the examining physician on the Driver's Declaration, they qualify for a ten year driving license, and a report by an ophthalmologist is required every ten years.
If the applicant suffers from chronic complications, e.g. to his eyes, heart or blood vessels, the driving ability is also assessed by using the chapter of the Annex in which the criteria with respect to the affected organ system are stipulated. In case of functional disorders of the limbs a CBR expert in the field of practical driving ability has to be consulted to perform a technical examination and/or a driving test.

[5] Stcrt. 1996, 81. Amended in Stcrt. 1996, 101; Stcrt. 2000, 99; Stcrt. 2002, 60; Stcrt. 2003, 188; Stcrt. 2004, 91.
[6] Source: Report CBR 2005.

To all forms of diabetes the rule of the Annex applies, that people who suffer from a sudden and unexpected decrease or loss of consciousness, are deemed *unfit* to participate in motorised road traffic regardless.

Which information is given to the CBR?

A diabetic applying for a driving license has to inform the CBR:

a) that he/she suffers from diabetes (since this always brings about a limitation of the period of validity);
b) about the medication with which he is treated (paragraph 5.2.2 t/m 5.2.4 of the Annex)
c) if he/she suffers from sudden and unexpected decrease of consciousness because of hypoglycaemias, and if the diabetes involves complications to the eyes, nervous system, heart or blood vessels.

To the CBR, the Driver's Declaration, which has to be filled out by the applicant, is the quintessential source of the information. However, only from people who apply for a driving license *for the first time* (through the Driver's Declaration which is filled out truthfully[7]), the CBR receives the information which leads to the issuing of a driving license of a limited period of validity according to the Annex. The CBR does not receive this information with regard to people who develop diabetes after passing their driving test. That is to say: not automatically.

These people may *voluntarily* (by virtue of article 124 section 1 under d WVW 1994) report the CBR about their diabetes and therefore the necessity to examine if they still possess the necessary physical fitness; there is, however, no *obligation* to inform CBR. The diabetic who develops (acute or chronic) complications which might affect his driving ability (e.g. sudden decreases of consciousness), is not obliged to report this to CBR either.

Given the consequences connected to informing the CBR according to the Annex (limitation of the period of validity of the driving license or even invalidity of the driving license), it is not surprising that the commitment to informing the CBR voluntarily about one's diabetes is not widely spread. The number of people developing diabetes was estimated at 37,500 in 2002[8]. The number of people informing the CBR about their doubts of their driving ability, amounts to a total of approximately 5,000, according to the CBR. Only 9% of the people who voluntarily inform the CBR have diabetes[9]. Apparently, the majority of the holders of a driving license developing diabetes or complications, do not inform CBR.

[7] By virtue of article 114 in connection with article 176 section 3 in connection with article 178 WVW 1994 the deliberately wrongful Driver's Declaration constitutes a crime which is penalised by a maximum prison sentence of three months or a third category fine.

[8] Ruwaard, Feskens E.J., [How often does diabetes mellitus occur and how many people die from it?] 2002, Bilthoven: RIVM. RIVM Studies of the Future of National Health Care, National Compass of National Health Care.

[9] Source: Report CBR 2004.

Acceptable risk?

By not a priori excluding diabetics from driving a motor vehicle and by not wielding the weapon of obligation to inform the CBR of the development of diabetes after passing their driving test, the legislator accepts the risk of road traffic accidents pursuant to the fact that the driver is suffering from diabetes (read: has a higher chance of suffering from hypoglycaemia).
Of course, the question is, whether this risk is acceptable or whether patients with diabetes should be excluded from the driving license. A variant to choice might be the situation in which only a certain part of the diabetic patients is excluded from the driving license, i.e. the group consisting of people with a (seriously) increased risk of road traffic accidents (read: severe hypoglycaemias). It has to be noted that the legislator apparently deems the current risk acceptable, since the large majority of diabetics is qualified for obtaining a driving license, albeit for a limited period of validity.
Remarkably, only few scientific studies have been performed into the relationship between diabetes and road traffic accidents. Some studies show that drivers with diabetes have a higher risk of being involved in road traffic accidents than drivers without diabetes, whereas other studies show that the risk is in fact lower. Most studies, however, conclude that no significant differences can be shown.
A closer examination of these studies, however, shows that in many cases validity of the findings is limited, since almost all studies suffer from methodological shortcomings, which may lead to both overestimation and underestimation of the number of road traffic accidents caused. As far as can be assessed, the increase in risk of road traffic accidents, if any, seems marginal.

Recent Dutch studies, assessing driving performance in a driving simulator of patients with diabetes with a normal blood glucose level and during moderate hypoglycaemia, indicate that patients with good hypoglycaemia awareness show good driving performance at the moment they clearly perceive (moderate) hypoglycaemia. To this group, not the occurrence of hypoglycaemia proper, but the decision to (continue to) drive is of paramount importance for the risk of road traffic accidents.
From the available studies, no specific subgroup of patients at increased risk of road traffic accidents can be identified. Theoretically, it is apparent that people having hypoglycaemia unawareness have the highest risk of causing a road traffic accident due to a severe hypoglycaemia.

The execution of the Regulations in practice

As indicated supra, by virtue of Annex to the Fitness Criteria Regulations 2000, a driving license with a limited period of validity of 10 years can be issued in case of a diabetic applicant. The driving license expires upon expiration of the period of validity (article 122 section 2 WVW 1994). By filing a new Driver's Declaration, the diabetic patients concerned can apply for a new Declaration of fitness (article 35 Driving Licenses Regulations). The criteria stipulated in the Annex apply to the application. Typically, the CBR follows the physician's report in the Driver's Declaration. If this report is satisfying (i.e. does not mention complications), no further examination takes place and the Declaration of fitness, which is necessary to obtain the driving license, is issued.
The examination of medical fitness is for the greater part conducted by filling out the Driver's Declaration by the examining physician or internist in stead of an examination by or by order of the CBR.

Section 5.2.1 of the Annex stipulates that people suffering from sudden and unexpected decrease of consciousness because of hypoglycaemia, are not fit to drive a motorised vehicle regardless. He can be declared fit again by virtue of the Annex, if the warning signals are present again, and if the patient is deemed sufficiently able to treat himself by a diabetes specialist.
Since, as mentioned supra, approximately 25% of the type 1 diabetics suffer from hypoglycaemia unawareness and therefore fall in the group mentioned in section 5.2.1 of the Annex, strict enforcement of this rule would mean exclusion of 25% of patients with type 1 diabetes from driving a motor vehicle. Approximately 2.5% of the type 2 diabetics would be excluded. Given the large number of patients with type 2 diabetes, the absolute number of people excluded from driving licenses in this category would be quite substantial.
Inquiry with the CBR learns that *in practice*, the examining physicians seldom mention impaired hypoglycaemia awareness in their report in the Driver's Declaration, causing the percentage of diabetics whose application for a group 1 driving license is turned down, to be very low: less than 1%[10].
From the fact that the CBR allows for such a large discrepancy between the statistic amount of applicants who presumably suffer from hypoglycaemia unawareness, and the actual amount of applicants of whom hypoglycaemia unawareness is reported, it can be deducted that CBR deems exclusion of a larger group of diabetics socially undesirable.

In the process of legislation a weigh of the pros and cons is made of, on the one hand, the higher risk of road traffic accidents because of diabetes, and, on the other hand, the impact of the exclusion of (a certain group of) patients from taking part in motorised road traffic, both on a personal and a social level. Currently, in the Netherlands approximately 440,000 people suffer from diabetes. There are strong indications that these numbers are rising. According to the most recent estimates over 300,000 newly diagnosed diabetic patients in the age group between 50-75 years are to be expected the next 4-6 years[11]. Possible changes in the (enforcement of the current)

measures concerning driving privileges, may have substantial social consequences. On the other hand, however, it is logical that with a rising amount of drivers in the risk group, the risk of hypoglycaemia related road traffic accidents will increase as well.

[10] Source: Report CBR 2004.

[11] Ruwaard D, Feskens E.J. OC

Bottlenecks in the current legislation

(Un)awareness

In drafting and executing the rules concerning driving privileges of patients with diabetes, or subgroups of this population, a number of complicating factors need to be taken in account:

a) The ability to recognise a hypoglycaemia may vary per patient from completely intact to completely absent, and everything in between: (un)awareness digresses along a sliding scale.
b) At any moment several different factors may influence the ability to recognise hypoglycaemia, including sleep, concentration, exertion (the patient needs to be able to distinct whether e.g. sweat or shaking is related to physical effort or to an impending hypoglycaemia).
c) It is very complicated to assess with medical certainty whether a person's hypoglycaemia awareness is "normal" or impaired. Assessment of (un)awareness requires a labour intense and burdening procedure, which can only be performed in specific research settings, and which is not (yet) suitable to be routinely performed on large numbers of patients. An alternative possibility is to use questionnaires to examine the (un)awareness. However, questionnaires have limited sensitivity and specificity, and can quite easily be subject to fraud.
d) The assessment of hypoglycaemia (un)awareness is only valid for a limited period of time. The variability of hypoglycaemia awareness implies the possibility of a sudden impairment of awareness (e.g. because of an unnoticed nocturnal hypoglycaemia whilst sleeping), or a rapid (within a few days to weeks) improvement of awareness because of the avoidance of hypoglycaemias during a certain period.
e) Monitoring of changes in (un)awareness is difficult, because the entire procedure with which the (un)awareness was assessed at any given time, needs to be performed again. Furthermore, nocturnal hypoglycaemias, which can impair awareness, can pass totally unnoticed. It also is unclear, how long a hypoglycaemia-free period must have expired after suffering from a severe hypoglycaemia (e.g. accompanied with a decrease of consciousness), before it can be concluded that the awareness is (possibly) (partially) restored. Currently there is no simple and reliable test, assessing hypoglycaemia awareness at any time, available. This means that, once one has been declared unfit due to unawareness, it is very difficult to be declared fit to drive again.

f) Lastly, patients whose hypoglycaemia awareness has always been completely normal (intact), can be subject to hypoglycaemia which they do not notice until it is impossible for them to take countermeasures. It is unclear, whether these occurrences are caused by prior (nocturnal) hypoglycaemias or by a disturbance of the awareness at a specific moment by unknown factors.

Duty to report

Inequality of justice By virtue of the current road traffic legislation, people who develop diabetes after passing their driving test, therefore having a higher risk of hypoglycaemia, are not obliged to inform the CBR, since informing by filing a new Driver's Declaration is explicitly voluntary. Article 124 section 1 under d WVW 1994 mentions the holder of a driving license who is no longer physically or mentally fit to drive a motorised vehicle "based on an examination conducted at his request".

This leads to the undesirable dichotomy between people who develop diabetes prior to passing their driving test and people who develop diabetes after passing their driving test. The former are obliged by virtue of section 5.2 of the Annex to undergo periodic examinations, if they want to extend their driving licenses, whereas the latter remain untouched until they reach the age of 70 years.

Should a driver who develops diabetes after passing his driving test, report himself voluntarily to the CBR, this might have unbeneficial consequences for his driving licence, which of course does not stimulate voluntary reporting.

However, there is a shadow side to not reporting one's diabetes voluntarily. If the driver who has developed diabetes after passing his driving test and who has not voluntarily reported in with the CBR for a re-examination, gets involved in a road traffic accident, this might have serious consequences with respect to the question of who is guilty. The driver has not (voluntarily) reported in for a re-examination, whilst this possibility existed, and whilst he (possibly!) knew that diabetes may affect driving ability.

The legislator pays for the legislated absence of the obligation to report in for re-examination. The driver might allege that he deducts from the legislator's indifference at this point that the re-examination is unnecessary. If it were necessary, the legislator would have stipulated that the re-examination be an obligation. The absence of the duty to report does not correlate with the position of the diabetic patient who has to fill out the Driver's Declaration prior to passing the driving test. For what reason does this dichotomy exist? In our point of view, a duty to report for drivers who have recently developed diabetes (i.e. after passing their driving test) seems logical. The Health Council endorsed our opinion in its 2002 report, advising the Minister (uninvitedly) to install a duty to report[12].

Duty to report, for the physician or the patient? If a duty to report newly diagnosed diabetes were to be installed, this duty could theoretically be imposed on two parties: the patient, and/or the physician who has made the diagnosis. If the physician is obliged to report his diagnosis to the public body issuing the driving license, as is the case in several Scandinavian countries, this duty forces the physician to breach his duty of confidentiality, stipulated in article 7:457 Dutch Civil Code. This means a breach of the relationship of confidentiality the physician maintains with his patient,

possibly damaging further treatment of the patient. Currently, a breach of confidentiality is only possible in the Netherlands in case of a serious threat to third parties, as can be the case for certain infectious diseases or e.g. a murder contemplated by the patient. Based on current data, whether diabetes constitutes such a serious threat to third parties, is highly dubious.

A duty to report for the physician might restrain a patient from seeking medical aid in case of a severe hypoglycaemia, or from reporting an occurred hypoglycaemia to the physician afterwards, thus hindering treatment, and possibly causing serious damage to the patient's health. Fundamentally, the physician is faced with the question, if the interest of traffic safety outweighs the interest of the patients not to be kept from seeking medical aid. Furthermore, it imposes a responsibility on the physician which could and should be borne by the patient to begin with. After all, it is the diabetic who bears the responsibility, if he applies for a driving license for the first time.
If the duty to report is imposed on the patient, on diagnosing diabetes the physician should inform the patient of the duty to report and the possible consequences of not reporting.

Serious complications, potentially affecting the driving ability, like severe hypoglycaemia, should be separately subject to an (distinctive) duty to report. This duty to report should be imposed on the patient, based on the aforementioned. With respect to the physician, the introduction of an obligation to supply verbal and possibly printed information to the patient might be very useful. This information may be laid down for example in a leaflet, in which the legal and practical aspects of diabetes and driving a motor vehicle are clarified.

[12] Health Council, "Driving ability of diabetics", The Hague: Health Council, 2002. information in the application for a driving license

What's next?

Given the lack of convincing evidence that the risk of causing road traffic accidents is higher among patients with diabetes, a reserved application of the current legislation, which is common practise at present, seems desirable. Further restrictions of the driving privileges would bring about severe social consequences, also because of the large amount of diabetics, which, in addition, is strongly rising. The CBR is aware of this and is not actively tracking patients with unawareness

In order to codify the current (desired) policy, it should be stipulated in the Annex more clearly, how to deal with impaired hypoglycaemia awareness. Clarity should be provided on the issues how hypoglycaemia awareness should be assessed, how the monitoring should take place, and when a patient could be considered fit to drive again. The basic assumption should be that only in case of a foreseeable or provable realistically and seriously increased risk of road traffic accidents, the inability to drive should be assumed.

Given the current undesirable and unfounded dichotomy between drivers who have developed diabetes before passing their driving test and drivers who develop diabetes after passing their driving test, a duty to report should be introduced also for drivers who develop diabetes after passing their driving test.

Enforcement can be ensured via the WVW 1994 by expanding the prohibition to supply false information in the application for a driving license stipulated in article 114 with a obligation to report relevant disorders after the driving license has been issued.

Technical solutions?

Solutions are conceivable, to minimalise the risk of a unannounced and unexpected hypoglycaemia by technical means, to the extent that people who would normally be denied driving ability due to unfitness, would be given the possibility to participate in traffic in a responsible way. There is a number of methods which measure the blood glucose level and may warn the driver for impending hypoglycaemia.
A first solution could be a certified blood glucose meter, which can record the blood glucose level measured, so that they can be read afterwards. This method demands that the driver regularly measures his blood glucose level, for example before every drive and every two hours whilst driving. This method might reduce the chance of a unexpected hypoglycaemia, albeit not completely nullify it, since a single measure of the blood glucose level does not indicate, whether the level at that moment is rising or falling. Furthermore, the blood glucose level can decrease very rapidly; measurement of a normal level therefore cannot guarantee the hypoglycaemia will not occur at all. Several other factors may influence the occurrence of hypoglycaemia, including the nature and size of the previous meal, the nature and quantity of medications used, the level of physical effort, heat, et cetera. In the United States of America, the effect of having the driver measure his blood glucose level before driving was studied, albeit in combination with behavioural training that can improve hypoglycaemia awareness. In this study a reduction of the number of road traffic accidents involving patients with diabetes has been shown. Clear guidelines and rules pertaining to the measurements should be incorporated in the legislation.
The method of the certified blood glucose meter, however, is fraud sensitive (it cannot be guaranteed that the driver's own blood was measured), invasive and stigmatising to the diabetic.

A second and in the future perhaps better applicable solution may be the use of a subcutaneously implanted glucose meter. These meters have been available for some years and measure the glucose level in the tissue fluid of, for example, the abdomen, by use of a small implanted sensor. The glucose level is registered by a meter outside the body. The currently available meters can only give a read-out afterwards, but it is technically well possible to provide a direct read-out on the machine and to install a warning signal in the machine, warning the driver for an impending hypoglycaemia, thus enabling him to take appropriate measures to prevent the hypoglycaemia in due time (i.e. pull over, stop the car and consume carbohydrates). It should be considered, however, that the glucose level in the tissue fluid corresponds with the glucose level in the blood (the level which directly concerns the functioning of the brain), albeit with a delay of 10-15 minutes. These glucose meters are also relatively new and not completely free or malfunctions. Nevertheless, in time, these meters may constitute a real solution to grant an application for a driving license in specific cases, in which current legislation leaves no room or only by high exception, as for example with group 2 driving licenses.
Nonetheless, this method, too, needs to be subject of research with respect to reduction of the risk of road traffic accidents and the execution and feasibility in practice.

Conclusion

The driving ability of diabetics is mainly influenced by the (risk of) occurrence of (not in due time recognised) hypoglycaemias. Scientific studies appear to show that the relative risk of road traffic accidents compared to road traffic accidents caused by non-diabetics, is only marginally increased. Moreover, recent studies indicate that the deciding factor for the risk of road traffic accidents, particularly in patients who recognise hypoglycaemias well and in due time, is not so much hypoglycaemia proper, but the decision to (continue to) drive.
Current legislation, if strictly executed, excludes large numbers of patients from obtaining their driving license, especially those who have reduced awareness of hypoglycaemia. In common practice, however, the criteria of the Annex to the Fitness Criteria Regulations 2000 are not strictly employed, therefore excluding only a limited number of diabetics from driving a motorised vehicle.
Problems in assessing (and dealing with) hypoglycaemia unawareness are its complexity, the possibility of rapid development of hypoglycaemia unawareness and its reversibility. Moreover, the assessment and monitoring of hypoglycaemia unawareness are extremely complicated and not (yet) suitable to be routinely performed.

Because of the absence of a duty to report diabetes for persons who have developed diabetes after passing their driving test, an unjust dichotomy exists between people who have developed diabetes prior to passing their driving test and people who have developed diabetes after passing their driving test. The introduction of a duty to report diabetes for all drivers seems a logical step. The duty to report diabetes should be imposed on the patients. The physician treating the patient should be obliged to inform the patient both verbally and through printed media on the legal and practical aspects of diabetes in connection with driving a motor vehicle.
Despite recent amendments, the Annex is due for further amending. With respect to the driving ability of diabetic patients, legislation needs to be brought in better accordance with the socially desirable standards, which are reflected by the current practical execution of the Regulations. This implies that further differentiations are required to the rule that persons suffering from sudden and unexpected decrease of consciousness caused by hypoglycaemia, are unfit to drive a motor vehicle regardless. This perspective is supported by the currently prevailing scientific views.
Technical means of assistance safeguarding driving ability in specific cases, may lead to further amendment of the Annex to the Fitness Criteria Regulations 2000, once they have been sufficiently developed.

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Chapter 9 Summary and conclusions

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In Chapter 1, the increasing importance of mobility, in particular automobile mobility, in modern society[1] is discussed. Moreover, there is an increasing number of elderly people[2], who, in addition, also show an increased mobility[3]. Simultaneously, the incidence of both type 1[4-6] and type 2 diabetes[7-9] is mounting throughout the world. Management of glucose homeostasis of these patients with diabetes is progressively aiming at near-normoglycaemia[10-12]. Consequently, the rate of hypoglycaemia, and thus the rate of hypoglycaemia unawareness, has increased[13-18]. This thesis is at the cutting edge of increasing automobile mobility and changes in incidence and treatment of diabetes.

In Chapter 2 the current state of affaires regarding diabetes and driving is reviewed, including the further studies needed to elucidate the relationship between diabetes and driving. Throughout the world, laws, rules and regulations regarding medical conditions have to balance individual interests on one side against the general interest of traffic safety on the other side, and therefore the safety risks of granting driving privileges to a certain group of people with a (possibly) increased risk of automotive accidents have to be estimated. Social as well as economic factors play an important role. In many countries, there are restrictions for diabetic drivers, ranging from more frequent than usual medical examination to denial of driving privileges for certain groups. In research on diabetes and driving, several study designs have been applied, each of which entails potential strengths and biases. Evaluation of the available research is difficult. Overall the available studies indicate that road traffic accidents directly caused by diabetes seem to be relatively rare occurrences. However, without a doubt hypoglycaemia during driving does occur, and can cause traffic accidents. If any trend can be distilled, current knowledge may point towards a slightly increased risk of road traffic accidents for drivers with diabetes mellitus. However, no subgroup that is particularly at risk has been unequivocally defined. The appraisal of potential risks of participation in traffic of a certain group of people, versus the social aspects of denying participation, may be influenced by society, media and experts, but final appraisal should be performed by the legislators. At this point in time, to increase current understanding, support decisions on legislation concerning diabetes and driving, and to tailor legislation to specific subgroups at risk, three types of research would be most helpful: First, a large, multi-centre, multinational, prospective follow-up study on the rates of traffic accidents and incidents of patients with diabetes in comparison to a well matched control group from the general population. Relevant diabetes-related information should be available, to identify specific subgroups at risk for road traffic incidents or accidents, including commercial drivers. Second, as programs such as Blood Glucose Awareness Training (BGAT), are potentially useful, future research should focus on their long-term efficacy, and the necessity of repetitive glucose awareness instruction. Third, research on driving performance of various groups and subgroups of patients with diabetes should be performed, preferably in a well validated state-of-the-art driving simulator. It should primarily focus on driving performance and on the influence of hypoglycaemia and hyperglycaemia. Subsequently, specific subgroups of patients with diabetes with impaired driving performance should be identified. Other driving simulator studies may investigate the impact of BGAT on driving performance. Finally, when subgroups of patients who are

at increased risk of road traffic incidents and accidents have been identified, research should subsequently focus on altering factors that influence the increased risk, including behavioural, pharmacological and technical possibilities.

In Chapter 3 studies concerning driving performance of type 1 diabetic subjects with normal and with impaired hypoglycaemia awareness, and the effect of moderate hypoglycaemia on driving performance are described. For this study, a highly validated, state-of-the-art driving simulator was used. Both groups of patients with type 1 diabetes drove safely under euglycaemic conditions, although perhaps slightly more effort was needed. However, the fact that driving performance was maintained must by itself be considered to be of primary importance. Moderate hypoglycaemia (2.7 mmol/l) did not influence driving performance or workload. Therefore there appears to be a 'window of action', i.e. a lag time between occurrence of warning symptoms and onset of impaired driving performance. This allows patients with normal hypoglycaemia awareness to take appropriate measures when moderate hypoglycaemia occurs during driving, before driving performance will inevitably decrease at lower blood glucose levels. However, in patients with impaired hypoglycaemia awareness, this window of action is probably more narrow or even absent, making these patients more at risk for suffering driving decrements, possibly leading to traffic incidents, even when well educated and responding adequately when symptoms of hypoglycemia occur. This problem can increase substantially in the near future, as a growing proportion of patients is treated with intensive insulin regimens, potentially leading to reduced hypoglycaemia awareness and an increased risk of severe hypoglycemia[19-21].

The incidence of type 2 diabetes mellitus is mounting throughout the world, affecting people at increasingly young age[7-9]. Management of these patients is progressively aiming at near-normoglycaemia, since this reduces diabetic complications. Moreover, insulin is used earlier in the course of the disease[11,12]. Consequently, the incidence of hypoglycemia, which is the limiting factor in achieving euglycaemia, increases. Hypoglycaemia appears to be more common in type 2 diabetes than previously presumed[15-18]. Therefore, we also performed a driving simulator-study in type 2 diabetic patients with normal hypoglycaemia awareness, which is described in Chapter 4. Similarly to the type 1 diabetic patients, type 2 patients also drove safely during euglycaemia. However, for reasons unclear, more effort was needed to accomplish this as compared to non-diabetic drivers. The effort needed to drive further increased during moderate, symptomatic hypoglycaemia, but safe driving was maintained. No subgroup with poorer driving performance could be identified.

The results as discussed in Chapters 3 and 4, including the 'window of action', suggest that the possible occurrence of hypoglycaemic (autonomic) symptoms immediately before or during driving in patients with normal awareness of hypoglycemia does not imply a risk per se. Due to the nature and known symptoms of hypoglycaemia, driving performance will inevitably deteriorate at lower levels of glycaemia. Therefore, the decision to initiate driving or to take appropriate action during driving (pull over and

consume carbohydrates) when hypoglycaemic, seems of paramount importance. This is further evaluated in Chapter 5. Before each driving session (euglycaemia (5.0 mmol/l) and hypoglycaemia (2.7 mmol/l)) of the studies in the previous two chapters, patients were asked whether they felt hypoglycaemic and whether they would currently drive. Most patients with type 1 diabetes with normal awareness of hypoglycemia appear to make safe decisions concerning hypoglycemia and driving. In contrast, patients with type 1 diabetes with impaired awareness of hypoglycemia frequently decide to drive while hypoglycaemic, which even if not totally unexpected is potentially dangerous. Strikingly, patients with type 2 diabetes and normal hypoglycaemia awareness frequently take potentially dangerous decisions as well, chiefly those using oral hypoglycaemic agents. This is particularly worrying in light of the increasing number of patients[7-9].

In traffic research, the Theory of Reasoned Action[22], later expanded to the Theory of Planned Behavior[23,24] is frequently used, and has been found to predict a range of road user behaviours[25]. It classifies a vast range of variables into only three categories, imposing some structure on attitude research. Using this theory, it can be explained that normative beliefs, based on the pressure to comply with social norms, have an effect on intentions in traffic (in this case: not driving when hypoglycaemic). Normative belief is significantly related to past behaviour and perceived behaviour of others. Moreover, well established behaviour is less affected by social pressure than less established behaviour[25]. Other studies indicate that the attitude towards the behaviour (i.e.: how does a person judge driving when hypoglycaemic) may also influence the choices that are made. There seem to be large cultural differences in the intention to comply with rules and regulations[26]. Considering the results as described in Chapters 3, 4 and 5, in line with accepted traffic psychology models, decision making of patients with diabetes in relation to hypoglycaemia may be positively modified using a number of interventions. Patients should be made aware repeatedly and explicitly of current recommendations by doctors and nurses. This may be done individually, but if done in group sessions, this will influence peer pressure and perceived behaviour by others. Moreover, education should be started in an early phase of the disease, before undesired behaviour has established. In patients developing diabetes at older age, established behaviour should be taken into account. Early, clear and consistent education is imperative for the safety of diabetic patients in modern traffic.

In diabetes research in general, and in research on the relationship between diabetes, hypoglycaemia, hypoglycaemia awareness and driving in particular, methodology is important. In the previous studies, establishment and maintenance of euglycaemia during a prolonged period of time was desirable. Moreover, overnight euglycaemia can be of use for initiation or adjustment of glucose lowering therapy, and to determine basal insulin requirements. Furthermore, in recent years evidence has become available showing the importance of near-normoglycaemia in the (critically) ill[27-32]. In Chapter 6 the safety and efficacy of a practical, bodyweight-dependent algorithm to establish euglycaemia in patients with diabetes is assessed. During a fasting period of approximately ten hours, euglycaemia was established simply, swiftly and safely with

the practical weight-based algorithm used in the study. The algorithm was applied in both lean and obese type 1 and type 2 diabetic patients who were otherwise healthy, with a very low rate of mild hypoglycaemia. The algorithm is applicable in research and various several clinical settings. Its validity for a prolonged period of time and in critically ill patients needs to be further evaluated.

A growing amount of research is performed in the field of diabetes, both in the laboratory and in the field. Therefore, there is an increasing need for an accurate, swift and easy to operate method of glucose determination. Most currently marketed hand-held devices for home glucose determination do not offer sufficient accuracy and precision, especially in the hypoglycaemic region, where accurate determination of glucose can be crucial for diagnosis and treatment[33-43]. The HemoCue glucose analyser is an instrument that is portable, can be used pre-analytically and bedside. As described in Chapter 7, the determination of glucose with the HemoCue showed very high correlation (and was virtually identical) to measurement with a glucose oxidase system which is often used as standard method in diabetes research (Yellow Springs Instruments), in a broad range of glycaemia, and in hypoglycaemia in particular. The results indicate that these methods can be used interchangeably for research and clinical purposes in adults.

To regulate motorised traffic, in most countries in the world driving licences are issued. In doing so, authorities and legislators attempt to the balance the interests of individuals (the liberty to operate a motor vehicle) against the interests of society (road safety). A variety of medical conditions and diseases, including diabetes, are presumed to negatively influence driving performance under certain conditions, as discussed in Chapter 2. Therefore, throughout the world, restrictive legislature concerning diabetic drivers has been issued. To explore the practical implications of the research described in this thesis, for patients with diabetes and for society, in Chapter 8 laws and regulations in the Netherlands concerning diabetes are studied. It appears that the Dutch law states that all patients with diabetes who suffer from sudden and unexpected loss of consciousness because of hypoglycaemia are unsuited for a driving licence. Consequently, all patients who have reduced hypoglycaemia awareness, i.e. 25% of all type 1 diabetic patients and a lower but still significant proportion of type 2 diabetic patients, should not be allowed to drive a motor vehicle. However, the Dutch executive agency, the Central Vehicle Licensing Agency (CBR), seldom receives notice of reduced hypoglycaemia awareness, and rarely refuses or revokes a licence for this reason. Thus, the CBR appears to judge exclusion of a large group of diabetic patients socially undesirable, and consciously tolerates the current situation. In drafting and execution of the laws and regulations, there are a number of complications, including the biological character of reduced hypoglycaemia awareness, and the complexity of determining (regain of) hypoglycaemia awareness. The question arises whether the Dutch regulations concerning diabetes and driving should be amended to be in accordance with the current policy of tolerance. Moreover, notification of diabetes and of reduced hypoglycaemia awareness to the CBR is not mandatory in the Netherlands. This leads to legal inequality of patients who acquire diabetes before obtaining their

driving licence and those who acquire diabetes after obtaining their driving licence. To abandon inequality, it may be argued that in the Netherlands, as in other countries, notification of diabetes should be mandatory, and the duty to report to the Licensing Agency should be with the patients.

In line with the current state of affaires, as discussed in Chapter 2, and the results of the studies in Chapters 3, 4 and 5, exclusion of large groups of diabetic patients seems socially undesirable, and does not seem required. However, there may be certain subgroups of diabetic patients who are particularly at risk to cause road traffic accidents. Identification of these groups remains difficult, and will require further research. In the Netherlands, and throughout the world, legislators, licensing agencies and medical advisors should thoroughly evaluate their legislature, and amend it according to current and emerging insights. Early, clear and consistent education is imperative, and perhaps its legal regulation may be considered.

In conclusion, in this thesis the current state regarding diabetes and driving is discussed, and recommendations for further research are made. Subsequently, studies are described, demonstrating that patients with type 1 diabetes with normal and with impaired hypoglycaemia awareness, as well as patients with type 2 diabetes with normal hypoglycaemia awareness, have normal driving performance during euglycaemia, as well as during moderate hypoglycaemia, although in type 2 diabetic patients more effort is required to do so. However, it is also shown that the decision not to drive during hypoglycaemia is not always adequately made in type 1 patients with impaired hypoglycaemia awareness and by type 2 diabetic patients, particularly when using oral hypoglycaemic agents. The importance of good and tailored patient education is stressed. For methodological purposes, a practical algorithm to establish and maintain euglycaemia is studied. Moreover, the HemoCue glucose analyser is studied, and it is shown that it can be used interchangeably with the frequently used standard glucose oxidase method. Finally, the Dutch law is discussed, and discrepancies between the law and its execution by the Central Vehicle Licensing Agency (CBR) is noted. Recommendations are made for legislators, licensing authorities and medical advisors in the Netherlands and throughout the world to evaluate their legislature, and amend it according to current and emerging insights.

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Hoofdstuk 9a Samenvatting en conclusies

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In Hoofdstuk 1 wordt het groeiend belang van mobiliteit, met name met de auto, in de hedendaagse maatschappij[1] besproken. Bovendien is er een stijgend aantal ouderen2, die, daarenboven, ook een toegenomen mobiliteit vertonen[3]. Tegelijkertijd stijgt de incidentie van zowel type 1[4-6] als type 2 diabetes[7-9] over de gehele wereld. Bij de regulatie van de glucose homeostase van deze patiënten met diabetes wordt in toenemende mate gestreefd naar waarden zo dicht mogelijk bij normoglycaemie[10-12]. Dit heeft tot gevolg dat het vóórkomen van hypoglycaemie, en bijgevolg het vóórkomen van hypoglycaemia unawareness, eveneens is toegenomen[13-18]. Dit proefschrift bevindt zich op het snijvlak van toegenomen automobiliteit en veranderingen in de incidentie en behandeling van diabetes.

In Hoofdstuk 2 wordt de huidige stand van zaken rondom diabetes en autorijden beschreven, alsmede de studies die in de toekomst noodzakelijk zullen zijn om het verband tussen diabetes en autorijden verder op te helderen. Over de gehele wereld dient de wet- en regelgeving betreffende medische rijgeschiktheid een balans af te spiegelen tussen het individueel belang enerzijds en het algemeen belang van verkeersveiligheid anderzijds, en derhalve dienen de veiligheidsrisico's van het rijgeschikt verklaren van een bepaalde groep mensen met een (mogelijkerwijs) verhoogd risico op verkeersongevallen te worden ingeschat. Hierbij spelen zowel sociale als economische factoren een rol. In vele landen gelden restricties voor automobilisten met diabetes, variërend van frequentere medische keuring tot het ontzeggen van de rijbevoegdheid van bepaalde groepen. Bij het onderzoek naar diabetes en autorijden zijn studies met verschillende opzet verricht, waaraan telkens zowel potentiële voordelen als ongewenste beïnvloeding van de resultaten verbonden zijn. Evaluatie van het beschikbare onderzoek is moeilijk. Alles overziend lijken de beschikbare studies erop te wijzen dat verkeersongevallen die direct veroorzaakt worden door diabetes relatief zelden vóórkomen. Het leidt echter geen twijfel dat er wel hypoglycaemieën vóórkomen tijdens het autorijden, en dat hierdoor ongevallen veroorzaakt kunnen worden . Als er al een trend kan worden waargenomen, dan lijkt de huidige kennis te wijzen naar een licht verhoogd risico op verkeersongevallen voor automobilisten met diabetes mellitus. Er is echter niet eenduidig een subgroep te definiëren die in het bijzonder een verhoogd risico loopt. De waardering van mogelijke risico's die verbonden zijn aan de verkeersdeelname van een bepaalde groep mensen, versus de sociale aspecten van het ontzeggen hiervan, kunnen worden beïnvloed door de maatschappij, media en experts, maar de uiteindelijke inschatting zou gedaan moeten worden door de wetgevers. Op dit moment zouden, om het huidige inzicht te vergroten, besluitvorming rondom diabetes en autorijden te ondersteunen en de wet- en regelgeving aan te passen aan specifieke subgroepen met een verhoogd risico, drie soorten onderzoek het meest nuttig zijn: Ten eerste, een groot, multi-centrum, multi-nationaal, prospectief follow-up onderzoek naar de ongevalsincidentie van patiënten met diabetes in vergelijking tot een goed samengestelde controlegroep uit de algemene populatie. Relevante aan diabetes gerelateerde informatie zou beschikbaar moeten zijn, om specifieke subgroepen met een verhoogd risico op verkeersongevallen te identificeren, en ook vrachtwagenchauffeurs zouden hierbij betrokken moeten worden. Ten tweede zou, daar programma's zoals Blood Glucose Awareness Training (BGAT)

mogelijk nuttig zijn, toekomstig onderzoek zich moeten richten op hun effectiviteit op langere termijn, en de noodzaak tot herhaalde instructie. Ten derde zou onderzoek naar de rijvaardigheid van verschillende groepen en subgroepen van patiënten met diabetes verricht moeten worden, bij voorkeur in een goed gevalideerde, moderne rijsimulator. Dit onderzoek zou zich met name moeten richten op rijprestaties en op de invloed van hypoglycaemie en hyperglycaemie. Vervolgens zouden specifieke subgroepen met verminderde rijvaardigheid moeten worden onderscheiden. Andere studies met behulp van een rijsimulator zouden de invloed van BGAT op rijvaardigheid kunnen onderzoeken. Tenslotte zou, wanneer er subgroepen van patiënten die een verhoogd risico op verkeersongevallen hebben geïdentificeerd zijn, het onderzoek zich moeten richten op het modificeren van factoren die het verhoogde risico beïnvloeden, waarbij gedacht kan worden aan gedragsmatige, farmacologische en technische mogelijkheden.

In Hoofdstuk 3 worden studies beschreven naar de rijvaardigheid van patiënten met type 1 diabetes met zowel normale als gestoorde hypoglycaemia awareness, en naar het effect van matige hypoglycaemie op hun rijvaardigheid. Voor deze studie werd een hoog gevalideerde, moderne rijsimulator gebruikt. Beide groepen patiënten met type 1 diabetes reden veilig onder euglycaemische condities, hoewel hiervoor mogelijk meer moeite moest worden verricht. Desalniettemin moet het feit dat de rijvaardigheid gehandhaafd bleef van elementair belang worden geacht. Matige hypoglycaemie (2,7 mmol/l) beïnvloedde de rijvaardigheid of werklast niet verder. Derhalve lijkt er een "venster" te zijn waarin actie kan worden ondernomen, dat wil zeggen een bepaalde tijd tussen het optreden van waarschuwingssymptomen en het begin van verminderde rijvaardigheid. Dit geeft patiënten met een normale hypoglycaemia awareness de mogelijkheid om passende maatregelen te nemen indien zich een matige hypoglycaemie voordoet tijdens het autorijden, voordat de rijvaardigheid onvermijdelijk zal afnemen bij lagere glucosewaarden. Bij patiënten met een verminderde hypoglycaemia awareness zal dit venster echter nauwer of zelfs geheel afwezig zijn, waardoor deze patiënten een hoger risico lopen op een verminderde rijvaardigheid, die mogelijk leidt tot verkeersongevallen, zelfs al zijn deze patiënten goed onderricht en reageren zij adequaat als zich symptomen van hypoglycaemie voordoen. Dit probleem kan in de nabije toekomst substantieel toenemen, daar een steeds groter deel van de patiënten wordt behandeld met intensieve insuline schema's, die kunnen leiden tot verminderde hypoglycaemia awareness en een verhoogd risico op ernstige hypoglycaemie[19-21].

De incidentie van type 2 diabetes stijgt over de gehele wereld, en treft mensen op steeds jongere leeftijd[7-9]. De behandeling van deze patiënten is steeds meer gericht op het bereiken van (bijna) normoglycaemische waarden, daar dit diabetische complicaties vermindert. Bovendien wordt insuline eerder in het beloop van de ziekte gebruikt[11,12]. Dientengevolge neemt de incidentie van hypoglycaemie, hetgeen de beperkende factor is in het bereiken van euglycaemie, toe. Hypoglycaemie lijkt vaker voor te komen bij patiënten met type 2 diabetes dan aanvankelijk werd aangenomen[15-18]. Daarom hebben we ook een rijsimulatorstudie bij patiënten met type 2 diabetes en een normale hypoglycaemia awareness verricht, hetgeen wordt beschreven in Hoofdstuk 4. Overeenkomstig de patiënten met type 1 diabetes, reden de patiënten met type 2 diabetes

ook veilig tijdens euglycaemie. Zij moesten echter, om onduidelijke redenen, meer moeite verrichten om dit te bereiken in vergelijking tot niet diabetische chauffeurs. Deze werklast nam verder toe tijdens matige, symptomatische, hypoglycaemie, maar het veilige rijgedrag werd gehandhaafd. Er kon geen subgroep met verminderde rijvaardigheid worden geïdentificeerd.

De resultaten zoals besproken in Hoofdstukken 3 en 4, alsmede het "venster" waarin actie kan worden ondernomen, suggereren dat het mogelijk optreden van hypoglycaemische (autonome) symptomen direct voor of tijdens het rijden bij patiënten met een normale hypoglycaemia awareness op zichzelf geen risico met zich meebrengt. Vanwege de aard en bekende symptomen van hypoglycaemie, zal het onvermijdelijk zijn dat de rijvaardigheid afneemt bij lagere glucosewaarden. Derhalve lijkt de beslissing om te beginnen met autorijden of om passende maatregelen te nemen tijdens het autorijden (naar de kant gaan en koolhydraten gebruiken) indien hypoglycaemie optreedt van het allergrootste belang. Dit wordt verder geëvalueerd in Hoofdstuk 5. Voor iedere rit in de rijsimulator (euglycaemie (5,0 mmol/l) en hypoglycaemie (2,7 mmol/l)) tijdens de studies in de vorige twee hoofstukken, werd aan de patiënten gevraagd of zij het gevoel hadden een hypoglycaemie te hebben en of zij op dat moment in het dagelijks leven zouden autorijden. De meeste patiënten met type 1 diabetes en normale hypoglycaemia awareness lijken veilige beslissingen te nemen over hypoglycaemie en autorijden. Patiënten met type 1 diabetes en gestoorde hypoglycaemia awareness daarentegen beslissen veelvuldig auto te rijden tijdens hypoglycaemie, hetgeen, zelfs indien niet geheel onverwacht, potentieel gevaarlijk is. Opvallende is dat ook patiënten met type 2 diabetes en normale hypoglycaemia awareness frequent potentieel gevaarlijke beslissingen nemen, voornamelijk diegenen die orale bloedglucose verlagende middelen gebruiken. Dit is met name verontrustend in het licht van het toenemende aantal patiënten[7-9].

In verkeersonderzoek wordt de Theory of Reasoned Action[22], later uitgebreid tot de Theory of Planned Behaviour[23,24], frequent gebruikt, en er is aangetoond dat deze divers gedrag van verkeersdeelnemers kan voorspellen[25]. De theorie classificeert een groot aantal variabelen in slechts drie categorieën, waardoor structuur wordt aangebracht in attitudeonderzoek. Met gebruikmaking van deze theorie kan verklaard worden dat normatieve overtuigingen, gebaseerd op de druk om te voldoen aan de sociale normen, een effect hebben op de voornemens in het verkeer (in dit geval: niet rijden tijdens een hypoglycaemie). Normatieve overtuigingen zijn significant gerelateerd aan gedrag in het verleden en waargenomen gedrag van anderen. Bovendien wordt sterk vaststaand gedrag minder beïnvloed door sociale druk dan minder vaststaand gedrag[25]. Andere studies wijzen erop dat de houding tegenover het gedrag (dat wil zeggen: hoe beoordeelt een persoon autorijden tijdens een hypoglycaemie?) mogelijk ook de keuzes die gemaakt worden beïnvloedt. Er lijken grote culturele verschillen te zijn tussen de voornemens om zich te houden aan de regels26. De resultaten zoals beschreven in Hoofdstuk 3, 4 en 5 in beschouwing nemend, zou, in overeenstemming met geaccepteerde verkeers-psychologische modellen, het beslissingsproces van patiënten met diabetes ten opzichte van hypoglycaemie positief gemodificeerd kunnen worden met een aantal interventies.

Patiënten zouden herhaaldelijk en expliciet bewust gemaakt moeten worden van de huidige aanbevelingen door dokters en verpleegkundigen. Dit kan individueel, maar indien dit gedaan wordt in groepssessies, zal dit de groepsdruk en het door anderen waargenomen gedrag beïnvloeden. De educatie moet bovendien in een vroeg stadium van de ziekte worden begonnen. Bij patiënten die op latere leeftijd diabetes ontwikkelen moet rekening gehouden worden met het feit dat hun gedragingen sterker vaststaan. Vroegtijdig, duidelijk en consequente educatie is noodzakelijk voor de veiligheid van patiënten met diabetes in het huidige verkeer.

In diabetesonderzoek in het algemeen, en in onderzoek naar de relatie tussen diabetes, hypoglycaemie, hypoglycaemia awareness en autorijden in het bijzonder, is methodologie belangrijk. In de voorafgaande studies was het bereiken en handhaven van euglycaemie gedurende een langere periode wenselijk. Verder kan nachtelijke euglycaemie nuttig zijn voor het initiëren of aanpassen van glucose verlagende therapie, alsmede voor het vaststellen van de basale insulinebehoefte. Bovendien is in is de afgelopen jaren het belang aangetoond van het nastreven van normoglycaemie in (kritisch) zieke patiënten[27-32]. In Hoofdstuk 6 wordt de veiligheid van een practisch, lichaamsgewichtafhankelijk algoritme om euglycaemie te bereiken bij patiënten met diabetes onderzocht. Gedurende een periode van tien uur vasten werd op eenvoudige, snelle en veilige wijze euglycaemie bereikt met het practische gewichtafhankelijke algoritme dat gebruikt werd in de studie. Het algoritme werd toegepast bij zowel slanke als obese type 1 en type 2 patiënten met diabetes die overigens gezond waren, met een zeer lage frequentie van milde hypoglycaemie. Het algoritme is toepasbaar in onderzoek en diverse klinische omstandigheden. De validiteit ervan voor een langere periode en bij (kritisch) zieke patiënten moet nog nader worden onderzocht.

Er wordt in toenemende mate onderzoek gedaan op het gebied van diabetes, zowel in het laboratorium als in de kliniek. Derhalve is er een toenemende behoefte aan een accurate, snelle en eenvoudig te bedienen methode voor de bepaling van glucose. De meeste draagbare apparaten die momenteel op de markt zijn bieden niet voldoende accuratesse en precisie, met name in het hypoglycaemische gebied, waar accurate bepaling van glucose cruciaal kan zijn voor de diagnose en behandeling[33-43]. De HemoCue glucose analyser is een draagbaar apparaat, dat pre-analytisch en aan het bed gebruikt kan worden. Zoals beschreven in Hoofdstuk 7, toonde de bepaling van glucose met de HemoCue een zeer sterke correlatie met (en was vrijwel identiek aan) meting met een glucose oxidase systeem, hetgeen vaak gebruikt wordt als standaardmethode in diabetes onderzoek (Yellow Springs Instruments), over een breed spectrum van glycaemie, en in hypoglycaemie in het bijzonder. De resultaten geven aan dat deze methodes uitwisselbaar zijn voor gebruik in onderzoek en klinische doeleinden bij volwassenen.

Om gemotoriseerd verkeer te reguleren, worden in de meeste landen van de wereld rijbewijzen afgegeven. Door dit te doen pogen de autoriteiten en wetgevers de belangen van individuen (de vrijheid om een motorvoertuig te bedienen) af te wegen tegen de belangen van de maatschappij (verkeersveiligheid). Van diverse fysieke

toestanden en ziekten, waaronder diabetes, wordt verondersteld dat zij onder bepaalde omstandigheden de rijvaardigheid negatief beïnvloeden, zoals besproken wordt in Hoofdstuk 2. Derhalve is over de gehele wereld beperkende wetgeving uitgevaardigd betreffende chauffeurs met diabetes. Om de practische implicaties van het onderzoek zoals beschreven in dit proefschrift, zowel voor patiënten met diabetes als voor de maatschappij, te onderzoeken, wordt in Hoofdstuk 8 de wet- en regelgeving in Nederland betreffende diabetes bestudeerd. Het blijkt dat de Nederlandse wet verklaart dat alle patiënten bij wie plotseling en onverwacht bewustzijnsdalingen optreden door hypoglycaemie zonder meer ongeschikt zijn voor het verkrijgen van een rijbewijs. Dientengevolge zouden alle patiënten die een verminderde hypoglycaemia awareness hebben, dat wil zeggen 25% van alle patiënten met type 1 diabetes en een lager maar nog steeds significant deel van de patiënten met type 2 diabetes, uitgesloten moeten worden van het besturen van een motorvoertuig. Het uitvoerend orgaan in Nederland, het Centraal Bureau Rijvaardigheidsbewijzen (CBR), ontvangt zelden melding van verminderde hypoglycaemia awareness, en het komt slechts sporadisch voor dat het een rijbewijs om deze reden weigert of intrekt. Derhalve lijkt het CBR het uitsluiten van een grote groep van patiënten met diabetes sociaal onwenselijk te achten, en bewust de huidige situatie te gedogen. Bij het opstellen en uitvoeren van de wet- en regelgeving doen zich een aantal problemen voor, waaronder het biologisch karakter van verminderde hypoglycaemia awareness en de complexiteit van het bepalen van (herkregen) hypoglycaemia awareness. De vraag rijst of de Nederlandse regelgeving betreffende diabetes en rijvaardigheid zou moeten worden aangepast om in overeenstemming te zijn met het huidige gedoogbeleid. Bovendien is melding van het krijgen van diabetes en van verminderde hypoglycaemia awareness in Nederland niet verplicht. Dit leidt tot wettelijke ongelijkheid tussen patiënten die diabetes ontwikkelen vóór het behalen van het rijbewijs en patiënten die diabetes ontwikkelen ná het behalen van het rijbewijs. Om een einde te maken aan deze ongelijkheid zou ervoor gepleit kunnen worden dat er in Nederland, zoals in andere landen, een meldingsplicht voor diabetes wordt ingesteld, en deze meldingsplicht aan het CBR zou moeten liggen bij de patiënten.

In overeenstemming met de huidige stand van zaken, zoals besproken in Hoofdstuk 2, en de resultaten van de studies in Hoofdstukken 3, 4 en 5, lijkt het uitsluiten van grote groepen patiënten met diabetes sociaal ongewenst en niet noodzakelijk. Er zouden echter bepaalde subgroepen van patiënten met diabetes kunnen zijn die in het bijzonder een verhoogd risico hebben op het veroorzaken van verkeersongevallen. Het identificeren van deze groepen blijft moeilijk, en hiervoor zal verder onderzoek noodzakelijk zijn. In Nederland, en over de gehele wereld, zouden wetgevers, uitvoerende instanties en medisch adviseurs de wetgeving grondig moeten herevalueren, en aanpassen volgens de huidige en groeiende inzichten. Vroegtijdige, duidelijke en consequente educatie is noodzakelijk, en wellicht kan overwogen worden dit wettelijk te reguleren.

Samenvattend wordt in dit proefschrift de huidige stand van zaken betreffende diabetes en autorijden besproken, en aanbevelingen voor de toekomst worden gedaan.

Vervolgens worden studies beschreven die tonen dat zowel patiënten met type 1 diabetes met intacte en gestoorde hypoglycaemia awareness, als patiënten met type 2 diabetes met intacte hypoglycaemia awareness, normale rijprestaties hebben tijdens zowel euglycaemie als tijdens matige hypoglycaemie, hoewel dit bij patiënten met type 2 diabetes meer inspanning vereist. Anderzijds wordt eveneens getoond dat de beslissing om geen auto te rijden tijdens hypoglycaemie niet altijd adequaat wordt genomen door patiënten met type 1 diabetes met een gestoorde hypoglycaemia awareness en door patiënten met type 2 diabetes, met name als zij orale bloedglucose verlagende medicatie gebruiken. Het belang van goede en individueel gerichte patiënteneducatie wordt benadrukt. Voor methodologische doeleinden wordt een practisch algoritme om euglycaemie te verkrijgen en te handhaven bestudeerd. Bovendien wordt de HemoCue glucosemeter bestudeerd, en wordt aangetoond dat deze meter uitwisselbaar is met de vaak gebruikte standaard methode met glucose oxidase. Tenslotte wordt de Nederlandse wet- en regelgeving aangaande diabetes en autorijden besproken, en er worden discrepanties beschreven tussen de wet en de practische uitvoering hiervan door het Centraal Bureau Rijvaardigheidsbewijzen (CBR). Er worden aanbevelingen gedaan voor wetgevers, uitvoerende instanties en medisch adviseurs in Nederland en elders in de wereld om hun wet- en regelgeving te herevalueren en deze aan te passen naar huidige en groeiende inzichten.

Referenties

Conform chapter 9

Lectures, abstracts and publications

De Dagen 2000, Nederlandse Internisten Vereniging (NIV), Veldhoven, April 27-28, 2000.
Poster presentation: *The influence of moderate hypoglycemia on driving performance of type 1 diabetic subjects.*

Scientific Meeting of the Dutch Society for Diabetes Research (NVDO), Arnhem, May 20, 2000.
Poster presentation: *The influence of moderate hypoglycemia on driving performance of type 1 diabetic subjects.*

The 18th Annual Meeting, Anglo-Danish-Dutch Diabetes Group (ADDDG), Brockenhurst, Hampshire, May 16-19, 2000.
Oral presentation: *The effect of moderate hypoglycemia on driving performance of type 1 diabetic subjects.*

The 60th Annual Scientific Sessions, American Diabetes Association (ADA), San Antonio, Texas, June 9-13, 2000.
Poster presentation in the President's Poster Session: *The effect of moderate hypoglycemia on driving performance of type 1 diabetic subjects.*

The 36th Annual Meeting of the European Association for the Study of Diabetes (EASD), Jerusalem, September 17-21, 2000.
Oral presentation: *Driving performance of hypoglycemia aware type 1 diabetic subjects during euglycemia and moderate hypoglycemia in a state-of-the-art moving-base driving simulator.*

International Diabetes Monitor. 36th EASD Meeting, Daily Review – Tuesday, September 19.
Extensive and contemplative version of "Driving performance of hypoglycemia aware type 1 diabetic subjects during euglycemia and moderate hypoglycemia in a state-of-the-art moving-base driving simulator.", invited by Editor–in-Chief.

International Diabetes Monitor. 36th EASD Meeting, Daily Review – Wednesday, September 20.
The β-cell in impaired glucose regulation.

International Diabetes Monitor. 36th EASD Meeting, Daily Review – Thursday, September 21.
Long-acting insulins – milestone or cosmetics?

The 61th Annual Scientific Sessions, American Diabetes Association (ADA), Philadelphia, Pennsylvania, June 22-26, 2001. Invited guest speaker on the symposium "Driving and hypoglycemia": *Results from the Diabetes And Driving Study: In the driving seat*

Metabool Utrechts Gezelschap, Utrecht, the Netherlands, September 24, 2001: *Diabetics in the driving seat*

Pieken & Dalen, de problematiek van hyper- en hypoglycaemie. Corporate sponsored convention for diabetes nurses (September 26, 2001) and diabetes specialists (November 24, 2001), Zeist, the Netherlands, September 26 and November 24, 2001: *Resultaten van de Diabetes And Driving Study: Achter het stuur of overstuur?*

The 18th Congress of the International Diabetes Federation (IDF), Paris, France, August 24-29, 2003.
Posterpresentation: *Driving performance of patients with Type 2 diabetes mellitus during euglycaemia and moderate, symptomatic hypoglycaemia.*

Farmacotherapeutical Convention Soesterberg, Soesterberg, November 3, 2003.
Diabetes mellitus type 2 en insulinetherapie in de eerste lijn.

Meet the Dutch experts in diabetes. Convention on the occasion of the 100e birthyday of Dr. F. Gerritsen, Zwolle, April 7, 2004. *Resultaten van de Diabetes And Driving Study: achter het stuur of overstuur?*

Farmacotherapeutisch Convention Soesterberg, Soesterberg, October 4, 2004.
Langwerkende insuline analoga in de behandeling van diabetes mellitus..

Farmacotherapeutisch Convention Almere, Almere, June 2, 2005.
Langwerkende insuline analoga in de behandeling van diabetes mellitus..

Stork ADM, Haeften TW van, Veneman TF. *Diabetes and driving: desired data, research methods and their pitfalls, current knowledge and future research.* Diabetes Care 2006;29:1942-1949.

Stork ADM, Sels JEM, Schouten van der Velden AP, Janssen WH, Martens MH, Haeften TW van, Erkelens, DW, Veneman TF. *Driving performance and effort needed to drive of patients with type 1 diabetes mellitus during euglycemia and moderate hypoglycemia in a state-of-the-art moving-base driving simulator. Submitted for publication.*

Stork ADM, Schouten van der Velden AP, Sels JEM, Janssen WH, Martens MH, Haeften TW van, Erkelens, DW, Veneman TF. *Type 2 diabetes mellitus and driving performance under euglycemic and hypoglycemic conditions. Submitted for publication.*

Stork ADM, Haeften TW van, Veneman TF. *The decision not to drive during hypoglycemia in patients with type 1 and type 2 diabetes, according to hypoglycemia awareness. Submitted for publication.*

Stork ADM, Erkelens DW, Veneman TF. *A safe and practical algorithm for induction and maintenance of prolonged euglycemia in patients with type 1 and type 2 diabetes.* Diabetes Res

Clin Pract 2006;72:251-257.

Stork ADM, Kemperman H, Erkelens DW, Veneman TF. Comparison of the accuracy of the HemoCue glucose analyzer to the YSI glucose analyzer, particularly in hypoglycaemia. Eur J Endocrinology 2005;153:275-281.

Stork ADM, Norenburg ARAL. *Wet- en regelgeving rondom diabetes mellitus en het rijbewijs: discrepatie tussen regels en uitvoering*. Verkeersrecht 2005;53:333-339.

Vragen en antwoorden voor niet-ingewijden

Vraag: Waarom was dit onderzoek nodig?

Antwoord: Diabetes mellitus (suikerziekte) is een ziekte die steeds vaker voorkomt, zowel type 1 (voornamelijk bij jonge mensen) als type 2 (voornamelijk bij mensen met overgewicht). Bij deze ziekte is de hoeveelheid suiker (glucose) in het bloed te hoog. De behandeling brengt, onbedoeld, met zich mee dat mensen met diabetes soms een te lage bloedsuikerspiegel kunnen krijgen (hypoglycaemie). Als dit het geval is zullen zij zich (zeer) onprettig voelen, en, omdat de hersenen alleen glucose als brandstof kunnen gebruiken, zullen zij niet goed meer kunnen denken. Bij een heel lage bloedsuikerspiegel kunnen zij buiten bewustzijn raken. Het is daarom goed voor te stellen dat het krijgen van een hypoglycaemie tijdens het autorijden kan leiden tot ongelukken. Omdat dit zo goed voorstelbaar is, gaat de wetgever in de meeste landen hier ook vanuit, en legt chauffeurs met diabetes verschillende beperkingen op, die variëren van een periodieke medische keuring tot het geheel uitsluiten voor bepaalde categorieën van het rijbewijs. Het wetenschappelijk onderzoek dat hier eerder naar gedaan is, toont echter lang niet altijd aan dat mensen met diabetes ook daadwerkelijk meer ongevallen veroorzaken in het verkeer, en bovendien kleven er aan veel van die onderzoeken nadelen, waardoor de resultaten niet representatief zijn. Zeker omdat er zo veel mensen met diabetes zijn, is het van belang dat we precies weten of het inderdaad zo is dat zij een grotere kans hebben op het veroorzaken van verkeersongelukken, zodat wetten en regels gemaakt kunnen worden die voor iedereen zo eerlijk mogelijk zijn.

Vraag: Waar gaat dit proefschrift over?

Antwoord: In dit proefschrift wordt van verschillende kanten gekeken naar diabetes en autorijden. Eerst wordt het onderzoek dat al eerder is verricht kritisch besproken, en aan de hand daarvan worden aanbevelingen gedaan voor verder onderzoek. Een deel van dit aanbevolen onderzoek is ook uitgevoerd. Om de rijvaardigheid van mensen met diabetes te onderzoeken, zowel in normale toestand als tijdens een hypoglycaemie, hebben ze gereden in een moderne rijsimulator bij TNO in Soesterberg, en is hen gevraagd wat voor beslissingen over autorijden ze in het dagelijks leven zouden nemen. Tenslotte is naar de huidige situatie in de Nederlandse wet- en regelgeving gekeken.

Vraag: Wat zijn de belangrijkste conclusies?

Antwoord: Mensen met diabetes lijken net zo goed auto te kunnen rijden als mensen zonder diabetes, hoewel zij hier misschien wel iets meer hun best voor moeten doen. Ook met een matig verlaagde bloedsuikerspiegel kunnen zij nog goed autorijden. Dit betekent dat een hypoglycaemie op zich niet gevaarlijk hoeft te zijn, als degene die dit overkomt achter het stuur maar de juiste maatregelen neemt (naar de kant gaan, stoppen en wat eten of drinken) voordat de bloedsuikerspiegel nog lager wordt. De meeste mensen met diabetes nemen de juiste beslissing om niet te gaan autorijden als ze een hypoglycaemie hebben, maar niet allemaal. Als de letter van de wet gevolgd zou worden, zouden veel mensen met diabetes geen rijbewijs mogen hebben. In de praktijk worden zij echter door het CBR gedoogd. Dit lijkt op grond van de resultaten uit eerder onderzoek en dit proefschrift terecht.

Vraag: Wat betekent dit voor mensen met diabetes?

Antwoord: De resultaten uit dit proefschrift betekenen niet dat mensen met een hypoglycaemie auto kunnen gaan rijden; een hypoglycaemie kan immers wel gevaar opleveren. Wel kan gesteld worden dat als iemand een hypoglycaemie krijgt tijdens het autorijden, diegene niet direct een gevaar op de weg is; als hij of zij de hypoglycaemie goed aan voelt komen, dan is er nog tijd om adequate maatregelen te nemen. Het belang van goede instructie over diabetes en autorijden door hulpverleners wordt nog eens benadrukt. Er lijkt derhalve geen reden om de huidige wetten en regels strenger te maken, maar eerder om ze te versoepelen, en wellicht meer op maat te maken voor verschillende groepen mensen met diabetes. Dit is in 2004 voor het laatst gedaan, nadat onder andere wijlen prof. Erkelens en dr. Veneman dit, als lid van een adviescommissie voor de Gezondheidsraad, adviseerden aan de Minister van Verkeer en Waterstaat. In Nederland, en eigenlijk over de gehele wereld, zou de wet- en regelgeving nog eens grondig tegen het licht gehouden moeten worden, en aangepast moeten worden aan deze en nieuwe inzichten. Het huidige beleid, zoals uitgevoerd wordt door het CBR, zou hierin moeten worden vastgelegd.

Appendix A

Bijlage behorende bij de Regeling eisen geschiktheid 2000 (paragraaf 3.3, paragraaf 5.2, hoofdstuk 6, paragraaf 7.6 en hoofdstuk 9)

Hoofdstuk 3. Stoornissen van het gezichtsorgaan

3.3 Beperkte geschiktheidstermijn

Beperking van de geschiktheidstermijn voor één of meer rijbewijscategorieën, aan te geven door de keurend oogarts, is aangewezen bij onder meer de volgende progressieve, doorgaans bilaterale oogaandoeningen:

– cataract
– glaucoom met gezichtsveldbeperking (of het bestaan van grote scotomen)
– degeneratieve en vasculaire netvliesaandoeningen
– progressief lijden van de nervus opticus.

Hoofdstuk 5. Inwendige ziekten

5.2 Diabetes mellitus

5.2.1 Algemeen

Voor alle vormen van diabetes mellitus geldt dat personen bij wie plotseling en onverwacht bewustzijnsdaling of bewustzijnsverlies door hypoglycemie optreedt zonder meer ongeschikt zijn voor alle rijbewijscategorieën. Iemand kan weer geschikt worden verklaard als de waarschuwingssignalen weer aanwezig zijn en het zelfzorggedrag door een diabetesdeskundige als adequaat wordt ingeschat.

Voor personen met diabetes mellitus met complicaties van de ogen (onder meer retinopathie en cataract) geldt tevens hoofdstuk 3 en voor personen met complicaties van hart en bloedvaten geldt tevens hoofdstuk 6.

Indien er functiestoornissen aan de ledematen zijn ontstaan als gevolg van neuropathie is een specialistisch rapport ter vaststelling van de mate van functiestoornis vereist. Bij stoornissen door vaatafwijkingen is een aantekening van de keurend arts voldoende. Voor een juiste oordeelsvorming dient bij functiestoornissen ook een deskundige op het gebied van de praktische geschiktheid (van de desbetreffende afdeling van het CBR) te worden geraadpleegd om de geschiktheid vast te stellen. Het CBR heeft hiervoor een uitvoerig protocol.

De geschiktheidstermijn bij ernstige functiestoornissen van de ledematen is na een positieve rijtest maximaal drie jaar.

5.2.2 Behandeling met middelen die doorgaans geen hypoglycemieën kunnen veroorzaken

a. groep 1: Personen die vrij zijn van complicaties kunnen op basis van de aantekening van de keurend arts worden goedgekeurd voor een termijn van maximaal tien jaar. Iedere tien jaar is wel een rapport van een oogarts noodzakelijk.
b. groep 2: Personen die vrij zijn van complicaties kunnen op basis van de aantekening van de keurend arts worden goedgekeurd voor een termijn van maximaal tien jaar. Iedere tien jaar is wel rapport van een oogarts noodzakelijk.

5.2.3 Behandeling met middelen die hypoglycemieën kunnen veroorzaken, anders dan insuline

a. groep 1: Personen die vrij zijn van complicaties, hypoglycemieën goed voelen aankomen, in staat zijn hiermee adequaat om te gaan en die geregeld worden gecontroleerd door een diabetesdeskundige kunnen op basis van de aantekening van de keurend arts worden goedgekeurd voor een termijn van maximaal tien jaar. Iedere tien jaar is wel een rapport van een oogarts noodzakelijk.
b. groep 2: Personen die vrij zijn van complicaties, hypoglycemieën goed voelen aankomen, in staat zijn hiermee adequaat om te gaan en die geregeld worden gecontroleerd door een diabetesdeskundige, kunnen

worden goedgekeurd voor een termijn van maximaal vijf jaar. Een onderzoek door een onafhankelijke internist is bij elke aanvraag vereist en iedere vijf jaar is tevens een rapport van een oogarts noodzakelijk.

5.2.4 Behandeling met insuline

a:. groep 1: Personen die vrij zijn van complicaties, hypoglycemieën goed voelen aankomen, in staat zijn hiermee adequaat om te gaan en die geregeld worden gecontroleerd door een diabetesdeskundige kunnen op basis van de aantekening van de keurend arts worden goedgekeurd voor een termijn van maximaal tien jaar. Iedere tien jaar is wel een rapport van een oogarts noodzakelijk.

b:. groep 2: Personen die insuline gebruiken komen vanwege Europese regels slechts in uitzonderlijke gevallen in aanmerking voor een rijbewijs van groep 2.

Van die gevallen is alleen sprake indien zij voldoen aan de volgende voorwaarden:

- zij moeten vrij zijn van complicaties van ogen, zenuwstelsel of hart en bloedvaten;
- zij moeten hypoglycemieën goed voelen aankomen en in staat zijn hiermee adequaat om te gaan;
- zij moeten aan zelfcontrole doen en een goed inzicht hebben in hun ziekte, en
- zij moeten geregeld worden gecontroleerd door een diabetesdeskundige.

Een onderzoek door een onafhankelijke internist is bij elke aanvraag vereist en iedere vijf jaar is tevens een rapport van een oogarts noodzakelijk.
De maximale geschiktheidstermijn is 3 jaar.

Hoofdstuk 6. Hart- en vaatziekten

6.1 Inleiding

Voor de geschiktheidsbeoordeling zijn (ook) bij hart- en vaatziekten van belang: de actuele lichamelijke conditie (al of geen klachten optredend bij deelname aan het verkeer), de voorgeschiedenis (aangeboren of verworven aandoening, status na operatie en dergelijke), en de prognose (kans op verergering van klachtenpatroon, kans op complicaties). Bij het formuleren van onderstaande eisen is met deze aspecten die nogal kunnen verschillen per type aandoening rekening gehouden. Voor de indeling van klachten naar ernst is de classificatie van de New York Heart Association (NYHA) gevolgd.

6.2 Chronisch hartfalen

Onvoldoende pompwerking van het hart (decompensatio cordis) kan berusten op een of meer oorzaken zoals aandoeningen genoemd in de hierna volgende paragrafen. Voor de specifieke criteria bij deze aandoeningen zij naar deze paragrafen verwezen. Is de oorzaak een andere dan hierna genoemd of is de oorzaak niet goed bekend, dan gelden in het algemeen de volgende richtlijnen.
Bij rijbewijzen van groep 1 is voor de geschiktheidsbeoordeling de aantekening van de keurend arts doorgaans voldoende. Voor groep 2 is steeds een specialistisch rapport vereist.
Bij personen met lichte tot matige klachten bedraagt de maximale geschiktheidstermijn voor groep 1 vijf jaar; zij zijn in het algemeen ongeschikt voor rijbewijzen van groep 2.
Personen met ernstige klachten (NYHA klasse 3 en 4) zijn ongeschikt voor ieder rijbewijs.
Voor transplantatie van hart en/of long(en): zie paragraaf 5.7.2.

6.3 Ischemische hartziekten

Het gaat hierbij om alle personen met kransvatlijden, ongeacht of zij daarvoor in behandeling zijn (geweest) of in het verleden een ingreep hebben ondergaan zoals een coronaire- bypass-operatie of een dotterbehandeling (PTCA). Van belang voor de geschiktheidsbeoordeling zijn het actuele klachtenpatroon al dan niet bij gebruik van medicatie en de prognose.

6.3.1 Asymptomatisch kransvatlijden

Het betreft personen bij wie aanwijzingen zijn gevonden bijvoorbeeld bij een inspanningstest (elektrocardiogram) voor het bestaan van kransvatlijden. In deze gevallen is steeds een specialistisch rapport vereist. De maximale geschiktheidstermijn bedraagt tien jaar.

6.3.2 Chronische stabiele angina pectoris

Bij rijbewijzen van groep 1 is voor de geschiktheidsbeoordeling de aantekening van de keurend arts voldoende. Voor groep 2 is steeds een specialistisch rapport vereist.

Bij personen met lichte tot matige klachten bedraagt de maximale geschiktheidstermijn voor groep 1 vijf jaar; zij zijn in beginsel ongeschikt voor rijbewijzen van groep 2.

Personen met ernstige klachten (NYHA klasse 3 en 4) zijn ongeschikt voor ieder rijbewijs.

6.3.3 Instabiele angina pectoris

Ongeschikt voor elk rijbewijs.

6.3.4 Hartinfarct

Personen die een hartinfarct hebben doorgemaakt zijn ten minste de eerste vier weken na het infarct ongeschikt. Of en in hoeverre zij na deze periode geschikt zijn, hangt af van het klachtenpatroon en van de prognose (zie ook vorige paragrafen).

6.4 Cardiomyopathie

Een specialistisch rapport is altijd vereist. Personen met beginnende cardiomyopathie kunnen met goede medicatie jaren gevrijwaard blijven van klachten. Bij goedkeuring (bij NYHA klasse 2 alleen voor rijbewijzen van groep 1; bij NYHA klasse 3 en 4 altijd ongeschikt) is de maximale geschiktheids-termijn vijf jaar voor groep 1 en drie jaar voor groep 2.

6.5 Klepafwijkingen (verworven of aangeboren, al dan niet een klepprothese).

De maximale geschiktheidstermijn voor beide groepen rijbewijzen is tien jaar. Bij personen met klachten is altijd een specialistisch rapport vereist.

Bij lichte tot matige klachten (NYHA klasse 2) is de maximale geschiktheids-termijn voor groep 1 vijf jaar; deze personen zijn in beginsel ongeschikt voor rijbewijzen van groep 2.

Personen met ernstige klachten (NYHA klasse 3 en 4) zijn ongeschikt voor elk rijbewijs.

6.6 Aangeboren gebreken van hart en grote vaten

Het gaat hierbij om gebreken als septumdefecten, open Ductus Botalli, transpositie van de grote vaten en coarctatio aortae. Personen bij wie het defect in de jeugd operatief is gecorrigeerd kunnen op latere leeftijd (andere) cardiovasculaire complicaties krijgen zoals hypertensie, cardiomyopathie of ritmestoornissen. Zij dienen uiteraard beoordeeld te worden op hun actuele klachten, niet op de eerdere conditie. Afzonderlijke vermelding verdienen, de mate en vorm van 'shunting' (zie hierna).

Links-rechts shunt

Personen zonder klachten zijn geschikt voor beide groepen rijbewijzen zonder termijnbeperking.

Bij lichte klachten: geschikt voor groep 1 voor beperkte duur tot maximaal tien jaar; voor groep 2 is een specialistisch rapport vereist.

Rechts-links shunt (cyanose)

Voor alle categorieën is een specialistisch rapport vereist. Bij goedkeuring geldt een beperkte geschiktheidstermijn tot maximaal vijf jaar voor rijbewijzen van groep 1 en maximaal drie jaar voor rijbewijzen van groep 2.

6.7 Ritme- en geleidingsstoornissen

6.7.1 Ritmestoornissen

Als de keurling geen of slechts geringe klachten heeft, is deze geschikt voor rijbewijzen van groep 1 voor een termijn van maximaal tien jaar; voor groep 2 is een specialistisch rapport vereist.

Ernstige klachten (zoals duizeligheid of bewustzijnsstoornissen, of NYHA klasse 3 en 4) maken de keurling ongeschikt voor elk rijbewijs.

6.7.2 Geleidingsstoornissen

Het gaat hierbij om aandoeningen als sick-sinussyndroom, bifasciculair bundeltakblok, of een tweede- of derdegraads AV-blok. In deze gevallen is steeds een specialistisch rapport vereist; de maximale geschiktheidstermijn bedraagt tien jaar. Personen met ernstige klachten zijn ongeschikt voor elk rijbewijs.

6.7.3 Pacemaker

Beperking van de geschiktheidstermijn tot maximaal tien jaar. Voor rijbewijzen van groep 2 is een specialistisch rapport vereist.

6.7.4 Implanteerbare cardioverter-defibrillator

Voor personen bij wie een implanteerbare cardioverter-defibrillator (ICD) is ingebracht, is altijd een specialistisch rapport van een cardioloog met kennis en ervaring op dit gebied vereist. Deze personen zijn ongeschikt gedurende een observatieperiode van twee maanden na implantatie. Blijkt aan het einde van deze periode dat het apparaat geen elektroshocks heeft afgegeven, dan wel dat zich tijdens stimulatie door de ICD geen ernstige hemodynamische problemen hebben voorgedaan, dan kunnen bedoelde personen voor een beperkte termijn geschikt worden verklaard voor rijbewijzen van groep 1. De maximale geschiktheidstermijn is vijf jaar. Wanneer een ICD in of na bedoelde observatieperiode één of meer stroomstoten heeft afgegeven, geldt ongeschiktheid. Blijkt uit specialistisch onderzoek dat deze elektroshocks terecht zijn afgegeven, dan is de betrokkene ongeschikt gedurende minimaal twee maanden na de laatste shock. In geval van misplaatste shocks zijn ICD-dragers ongeschikt, totdat de kans op dergelijke shocks voldoende is gereduceerd door het opnieuw afstellen van de ICD. Het laatste moet blijken uit een observatieperiode van minimaal twee maanden na herafstelling van de ICD. Personen met een ICD zijn in alle gevallen ongeschikt voor rijbewijzen van groep 2.

Strenge eisen moeten worden gesteld aan aanvragers van een rijbewijs van groep 1, die dit rijbewijs beroepsmatig gebruiken. Zij zitten vele uren achter het stuur en dragen grote verantwoordelijkheden. Dragers van een ICD kunnen daarom in beginsel alleen geschikt worden verklaard als het gebruik wordt beperkt tot privé-gebruik.

In individuele gevallen kan een uitzondering worden gemaakt op de beperking tot privé-gebruik voor een termijn van maximaal vijf jaren en kan het rijbewijs ook worden gebruikt voor bepaalde vormen van beroepsmatig gebruik. Voorwaarde is keuring door een specialist en een verklaring van de werkgever waaruit blijkt dat niet meer dan vier uren per dag beroepsmatig gebruik wordt gemaakt van het rijbewijs. Deze uitzondering is niet mogelijk indien het beroepsmatig gebruik betrekking heeft op het vervoeren van personen of het onder toezicht doen besturen van derden.

6.8 Perifere vaatziekten

6.8.1 Veneuze aandoeningen

Personen met een ernstige vorm van diep veneuze trombose zijn in het algemeen ongeschikt voor elk rijbewijs; in ieder geval is een specialistisch rapport vereist. Bij alle andere aandoeningen in deze rubriek geldt geschiktheid voor beide groepen rijbewijzen, tenzij er sprake is van bijzondere complicaties (ter beoordeling van een specialist).

6.8.2 Arteriële aandoeningen

Het betreft hier aandoeningen als aneurysma aortae, uitgebreide arteriosclerose, ziekte van Raynaud, de ziekte

van Buerger en scleroderma. Voor de geschiktheidsbeoordeling kan volstaan worden met de aantekening van de keurend arts. Personen die al dan niet na behandeling geen of geringe klachten hebben kunnen worden goedgekeurd voor rijbewijzen van groep 1 met een maximale termijn van tien jaar, en voor rijbewijzen van groep 2 met een termijn van vijf tot tien jaar.

6.9 Onbegrepen, mogelijk circulatoir veroorzaakte syncope

Personen met dergelijke klachten zijn ongeschikt voor alle rijbewijzen zo lang de diagnose onzeker is en er geen effectieve behandeling is ingesteld (of anderszins de klachten verdwijnen). Voor groep 1 geldt een klachtenvrije periode van een jaar, voor groep 2 van vijf jaar. Zie ook paragrafen 7.3 en 8.5.

Hoofdstuk 7. Neurologische aandoeningen

7.6 Doorbloedingsstoornissen van de hersenen

Doorbloedingsstoornissen van de hersenen omvatten beroerten (hersenbloeding of herseninfarct, ook wel CVA), TIA's (transient ischemic attacks), verwijdingen van slagaders (aneurysmata) en andere vaatmisvormingen van de hersenvaten.

7.6.1 Rijbewijzen van groep 1

Strenge eisen moeten worden gesteld aan aanvragers van een rijbewijs van groep 1, die dit rijbewijs beroepsmatig gebruiken (bijvoorbeeld taxichauffeurs, chauffeurs van busjes voor personenvervoer, maar ook voor het onder toezicht doen besturen van een motorrijtuig door een derde). Zij zitten vele uren achter het stuur en dragen grote verantwoordelijkheden. Aan hen moeten daarom dezelfde eisen worden gesteld als aan personen met een groep 2-rijbewijs. Aanvragers van een groep 1-rijbewijs die niet tevens voldoen aan de eisen voor groep 2, kunnen daarom in beginsel alleen geschikt worden verklaard als het gebruik wordt beperkt tot privé-gebruik.

In individuele gevallen kan een uitzondering worden gemaakt op de beperking tot privé-gebruik voor een termijn van maximaal vijf jaren en kan het rijbewijs ook worden gebruikt voor bepaalde vormen van beroepsmatig gebruik. Voorwaarde is keuring door een specialist en een verklaring van de werkgever waaruit blijkt dat niet meer dan vier uren per dag beroepsmatig gebruik wordt gemaakt van het rijbewijs. Deze uitzondering is niet mogelijk indien het beroepsmatig gebruik betrekking heeft op het vervoeren van personen of het onder toezicht doen besturen van derden.

7.6.1.1 Aneurysmata en andere misvormingen van de hersenvaten

A. *Toevallig ontdekte aneurysmata en andere misvormingen van de hersenvaten met kans op optreden van hersenbloedingen, maar die nog niet hebben gebloed.*

   Wanneer er geen behandeling is geweest, gelden wegens de relatief geringe kans op bloedingen geen beperkingen van de geschiktheid.

   Na een behandeling gelden de eisen onder B.

   Voor personen met epilepsie geldt tevens paragraaf 7.2.

B. *Aneurysmata en andere misvormingen van de hersenvaten die zijn ontdekt na bloedingen.*

   Personen met een aneurysma of een andere misvorming van de hersenvaten die gebloed heeft, zijn niet geschikt voor rijbewijzen van groep 1 tot zes maanden na de behandeling.

   Voor deze personen is een specialistisch rapport vereist om geestelijke of lichamelijke functiestoornissen vast te stellen. Als er geen functiestoornissen zijn, bestaat er geschiktheid voor onbepaalde tijd.

   Bij functiestoornissen volgt altijd een rijtest met een deskundige op het gebied van de praktische geschiktheid (van de desbetreffende afdeling van het CBR) en bij een positieve rijtest is de maximale geschiktheidstermijn vijf jaar. Het CBR heeft voor de rijtest een uitvoerig protocol.

   Voor personen met epilepsie geldt tevens paragraaf 7.2.

7.6.1.2 TIA en beroerte

Een TIA geeft geen beperkingen aan de geschiktheid.

Na een beroerte is men ongeschikt voor rijbewijzen van groep 1 voor een periode van zes maanden. Na die termijn is een specialistisch rapport vereist, opgesteld door een neuroloog of een revalidatiearts.

Bij afwezigheid van geestelijke of lichamelijke functiestoornissen bestaat geschiktheid voor onbepaalde tijd. Als er functiestoornissen aanwezig zijn volgt een rijtest met een deskundige op het gebied van de praktische geschiktheid (van de desbetreffende afdeling van het CBR). Bij een positieve rijtest is de maximale geschiktheidstermijn 5 jaar. Het CBR heeft voor de rijtest een uitvoerig protocol.

Voor personen met epilepsie geldt tevens paragraaf 7.2.

7.6.2 Rijbewijzen van groep 2

7.6.2.1 Aneurysmata en andere misvormingen van de hersenvaten

A. Personen met een onbehandeld aneurysma of onbehandelde misvorming van de hersenvaten zijn ongeschikt voor rijbewijzen van groep 2. Een uitzondering geldt voor toevallig ontdekte onbehandelde aneurysmata kleiner dan 10 mm. Deze personen zijn geschikt indien het specialistisch rapport gunstig is. De maximale geschiktheidstermijn is drie jaar
B. Personen met een behandeld aneurysma of behandelde misvorming van de hersenvaten zijn zes maanden na de behandeling weer geschikt voor rijbewijzen van groep 2, indien er blijkens een specialistisch rapport geen geestelijke of lichamelijke functiestoornissen zijn. De maximale geschiktheidstermijn is drie jaar.
C. Personen met een behandeld aneurysma of behandelde misvorming van de hersenvaten, die zes maanden na de behandeling blijkens een specialistisch rapport geestelijke of lichamelijke functiestoornissen hebben, zijn ongeschikt voor rijbewijzen van groep 2. Zij kunnen weer geschikt worden verklaard als zij, blijkens een specialistisch rapport, minimaal vijf jaar vrij zijn van functiestoornissen. De maximale geschiktheidstermijn is dan drie jaar.

   Voor personen met epilepsie geldt tevens paragraaf 7.2

7.6.2.2 TIA en beroerte

Na een TIA of beroerte zijn personen ongeschikt voor rijbewijzen van groep 2 voor een periode van vijf jaar.

Zij kunnen na deze periode weer geschikt worden verklaard als uit het neurologisch rapport blijkt dat zij vrij zijn van geestelijke of lichamelijke functiestoornissen. De maximale geschiktheidstermijn is drie jaar.

Voor personen met epilepsie geldt tevens paragraaf 7.2

Hoofdstuk 9. Lichamelijke handicaps

De geschiktheid van personen met een lichamelijke handicap wordt in eerste instantie beoordeeld door het CBR op basis van de aantekening van de keurende arts op de eigen verklaring en de eventueel reeds beschikbare overige gegevens (bijvoorbeeld een rapport van de revalidatiearts).

In de tweede plaats kan het CBR een beoordeling vragen door een deskundige op het gebied van de praktische geschiktheid van het CBR. Deze deskundige adviseert het CBR veelal na uitvoering van een technisch onderzoek of een rijtest over de mogelijkheden van de aanvrager van het rijbewijs om, zo nodig met aanpassingen aan het voertuig, een motorrijtuig te besturen.

Bij twijfel over de geschiktheid van de betrokkene in de nabije toekomst dient een beperkte geschiktheidstermijn voor de desbetreffende rijbewijscategorie te worden gehanteerd. Het CBR kan dan tijdig de geschiktheid opnieuw bezien.

Dankwoord

Alexander D.M. Stork

Dankwoord

D. Willem Erkelens Geachte professor Erkelens, beste Willem, al snel na het begin van onze samenwerking had ik het gevoel 'Willem' tegen je te willen zeggen. Je vaderlijke toon, elan, joie de vivre, en warmte gaven een familiair gevoel, net als je briefjes ondertekend met 'Willem'. Maar omdat je nooit daadwerkelijk zei "Zeg maar Willem." heb ik dat ook niet gedaan, en daar heb ik eigenlijk spijt van. Daarom ben ik blij dat ik dat nu alsnog kan doen. Vanaf ons allereerste gesprek heb ik het gevoel gehad dat je vertrouwen in me stelde. Ik weet nog de verbazing die ik voelde toen je me feitelijk een promotie- en opleidingsplaats had aangeboden, en ik stond te springen om "Ik doe het!" te roepen, en jij mij zei dat ik er eerst maar eens een nachtje over moest slapen. Die nacht heb ik heerlijk geslapen, en de volgende ochtend wist ik het nog steeds. Tijdens het traditionele AZU diner op de EASD 1998 in Barcelona, waar ik meteen naartoe mocht en we samen met je vrouw niet alleen over het vak spraken maar ook over voetbal en andere sport, was het pleit definitief beslecht. In de jaren die daarop volgden heb ik veel van je geleerd. Naast wetenschap en later ook klinische interne geneeskunde is het 'One Upmanship' daarvan het belangrijkste geweest. Degenen die niet weten wat One Upmanship is hebben niet het voorrecht gehad je te kennen. Ik ben altijd die warmte en dat vertrouwen blijven voelen, hoewel ik weet dat er af en toe momenten zijn geweest dat je eraan getwijfeld hebt of ik dit proefschrift ooit af zou kunnen maken. Het vervult me dan ook met trots dat het nu gelukt is, maar met pijn dat jij er niet meer bij bent.

Prof. dr. E. van der Wall Geachte professor Van der Wall, onder vervelende en ongebruikelijke omstandigheden was u bereid om de begeleiding van dit proefschrift als promotor op zich te nemen. Alle onderzoeken, die liggen op een gebied dat eigenlijk niet helemaal het uwe is, waren al klaar, en u moest er 'alleen nog maar' voor zorgen dat ik zou schrijven. Dat was voorwaar geen gemakkelijke opgave, maar steeds wist u mij door gerichte afspraken en de juiste woorden zo te prikkelen, dat het uiteindelijk toch gelukt is om dit proefschrift af te maken. Gevoel voor de menselijke en emotionele kant gingen daarbij hand in hand met uw enorme ervaring met publiceren. Ik voel veel dankbaarheid en respect voor de wijze waarop u dat gedaan heeft.

Thiemo Veneman Beste Thiemo, ik denk dat dit speciale project alleen bedacht kon worden door bijzondere mensen zoals Willem, Timon en jij. Het was fantastisch dat je met in het verdere beloop zo'n enorme vrijheid hebt. "Het is jouw onderzoek." zei je vaak, maar dat is natuurlijk niet helemaal waar. De afstand Utrecht-Almelo bleek eigenlijk geen probleem, want wat moest gebeuren gebeurde, desnoods telefonisch of per e-mail. Tijdens onze besprekingen, waarvoor je af en toe met meer dan toegestane snelheid mijn kant op reed, en ik soms naar Almelo, kwam heel wat meer naar boven dan alleen DADS. Ik kan me niet voorstellen dat andere onderzoekers zo met hun co-promotor zitten te praten. Golfen in San Diego was voor mij een hoogtepunt, en het was een absoluut wonder dat we niet met dat golfkarretje zijn omgeslagen. Dieptepunt was het moment waarop ik je, ieder rijdend in een Trabant door Boedapest, de middelvinger wilde geven, maar dat deed tegen een respectabele collega uit Hilversum. Ik hoop dat we samen te zijner tijd nog andere projecten zullen doen. L&l.

Timon van Haeften Beste Timon, jij hebt helemaal aan de wieg gestaan van dit project, lang geleden, samen met Willem en Thiemo. Daarom vind ik het ook erg leuk dat je ons later bent komen versterken. Je bent voor het voltooien van dit proefschrift van grote waarde geweest. Jouw nuchtere wetenschappelijke kijk is af en toe nodig geweest om mij, breedsprakig als ik ben, met beide benen op de grond te houden. Toen ik bij jouw gezellige gezin was, vroeg één van je dochters eens: "Hoe schrijven jullie nou samen. Doen jullie om de beurt een bladzijde?" Toen heb ik haar geantwoord: "Nee, het gaat anders. Ik schrijf dertig bladzijden en je vader schrapt er weer vijfentwintig." Af en toe deed het me gewoon pijn om de woorden waar ik zo hard op geploeterd had door jou doorgestreept te zien worden. En je genoot er nog van ook! Maar jouw ingrepen zijn de kwaliteit van dit proefschrift absoluut ten goede gekomen, en ik dank je hiervoor heel hartelijk.

Jan-Willem Sels Beste Jan-Willem, ik denk dat ik me geen betere vriend had kunnen wensen tijdens alle proeven dan jou. Naast je welhaast spreekwoordelijke zuidelijke gezelligheid (als je met je familie aan de telefoon zat kon ik je nauwelijks verstaan), bleek je ook over enorm veel lef en (bijna Amsterdamse) bluf te beschikken en een nog grotere mond te hebben dan ik. Maar (vrijwel) nooit was het ongegrond. Want je bent ook nog eens heel intelligent, met een enorm analytisch vermogen. De materie heb je je zeer snel eigen gemaakt, en we hebben er geweldig over kunnen discussiëren. Allemaal ideale eigenschappen lijkt mij, nog steeds, voor een internist. Als je vóór je opleiding tot cardioloog al weet dat je met name ritme en geleidingscardiologie wilt doen, zegt dat veel. Uiteindelijk heb ik er vrede mee, omdat ik zeker weet dat je in een heel goede cardioloog wordt.

Arjan Schouten van der Velden Beste Arjan, ik had niet gedacht dat ik dat ooit tegen een man zou zeggen, maar ontzettend bedankt voor al die nachten samen. Vanaf de eerste ontmoeting was je gezellig, hartelijk, betrokken en leergierig, maar nooit overmoedig. Je hebt in korte tijd heel goed leren clampen, en ik kon de clamp steeds met een gerust hart aan je overlaten. Toen het er echt om ging, en we noodgedwongen met z'n tweeën over bleven voor een ondoenlijke hoeveelheid nachtelijke studies, hebben we tegen elkaar gezegd: "Dit gaat natuurlijk nooit lukken, maar we kijken wel hoe ver we komen." We hebben het geprobeerd, we hebben het met een grote portie wilskracht volgehouden, en we hebben niet één patiënt af hoeven zeggen wegens slaapgebrek. En het was nog heel gezellig ook. Zonder jouw hulp was het onmogelijk geweest voldoende patiënten te onderzoeken. Ik heb grote bewondering voor je trouw, inzet en doorzettingsvermogen, en ik weet zeker dat je een geweldige oncologisch chirurg wordt. Heel veel dank.

José van Driel, Saskia Nijssen, Heleen Bussé van Oud-Alblas en Lisette C. von Vaupel Klein Ook jullie hebben me fantastisch geholpen met de nachtelijke euglycaemie, de clamps en alle zaken erom heen. Geweldig hoe jullie je geheel belangeloos zo hebben ingezet. Het ga jullie allemaal goed. En Heleen en Lisette: wat hebben jullie toch een prachtige namen.

Wiel Janssen Beste Wiel, we hebben wat met elkaar te stellen gehad! Eerst kwamen wij met van die enge ideeën, wilden jij de proeven weer helemaal anders. Je vond dat er twee controle groepen (waarom geen drie?) moesten komen, ik wilde meer onderzoeksgroepen. Dat werd weer te duur en te langdurig. Steeds maar weer wilde ik van alles het waarom begrijpen. Met een welhaast oneindig geduld heb jij mij, domme dokter, telkens weer uitgelegd hoe de dingen in elkaar zaten. Waarom de resultaten waren zoals ze

waren. Suggesties, referenties en feiten aangedragen. En bijna steeds had jij natuurlijk gelijk. Ik kwam terecht in een voor mij geheel nieuwe wereld, waar ik een beetje ingevoerd ben geraakt, en ik denk dat dàt juist het leukste is geweest aan mijn onderzoek. Dank je voor je inzet, betrokkenheid, geduld, en voor de harmonie waarin dat allemaal is gegaan.

Marieke Martens Lieve Marieke, wat voor Wiel geldt, geldt ook voor jou. Steeds kon ik rekenen op je inzet en steun. En op heel veel gezelligheid. Ondanks de ongure tijden en het harde werken ben ik altijd met veel plezier naar TNO gekomen. Om dan weer te horen hoe jij je met een parachute in de diepte had gestort (en weer op je pootjes terecht was gekomen), of iets anders wilds had gedaan. Doe je wel voorzichtig?

Wietze Hoekstra Beste Wietze, ik heb gezien hoe hard er geploeterd moet worden om zo'n rijsimulator in de lucht te houden. Ik geloof dat ik 'm maar een paar keer in de soep gedraaid heb, en dat die andere keren spontaan zijn gegaan. Maar telkens was jij er om alles weer aan de praat te krijgen. Overdag, 's morgens vroeg, maar ook 's avonds laat, als wij begonnen met de avondsessie, en de simulator niet deed zoals het hoort. Hoe vaak heb ik je niet bij je vrouw en kinderen of bij je andere avondjes vandaan gebeld? Maar nooit was je chagrijnig, altijd vrolijk en vooral gezellig. Dank voor al je inzet.

Medewerkers TNO-Technische Menskunde Soesterberg In het begin hebben jullie nog even moeten wennen, dat er plotseling een vreemde eend in de bijt (een dokter nog wel, die van die enge proeven deed) veelvuldig over de vloer kwam. Maar na verloop van tijd hebben jullie ervoor gezorgd dat ik werkelijk thuis was op jullie instituut. Ik heb er denk ik meer nachten doorgebracht dan wie dan ook. Dat mijn toegangspasje het een paar keer niet deed, en ik benaderd werd door de Marechaussee of ik hier wel hoorde mag een detail genoemd worden. Uitgenodigd worden op het TNO-TM feest vond ik een grote eer.

Hans Kemperman Beste Hans, jij hebt mij geholpen om van een artikel van een klinische dokter een echt artikel over een klinisch-chemisch onderwerp te maken, dat gepubliceerd kon worden. Zonder jou geen hoofdstuk 7. Dank daarvoor.

Adriaan Norenburg Beste Adriaan, nadat ik een beetje bij heb mogen dragen aan de juridische ondersteuning van een hypoglycaemische chauffeur, kwamen we erachter dat de wet- en regelgeving in Nederland eigenlijk heel anders is dan de daadwerkelijke –en eerlijkere– uitvoering in de praktijk. Dit bracht jou op het idee van een gezamenlijk artikel, dat over de grenzen van mijn vakgebied heen ging, en voor mij een extra dimensie geeft aan dit proefschrift. Hoeveel uren hebben we niet gewerkt aan de 13(!) versies van het artikel? Steeds weer maakte je mij duidelijk dat datgene, waar ik van dacht dat het helder uiteengezet was, zelfs voor een ingewijde, intelligente jurist nog niet goed te begrijpen was. Dank voor je inzet.

Harold de Valk Beste Harold, buiten het feit dat wij het op verschillende bijeenkomsten in binnen- en buitenland altijd heel gezellig hebben gehad, ben ik me ervan bewust dat jij waarschijnlijk degene bent die mijn onderzoek, en daarmee dit proefschrift, hebt gered. Op het juiste moment wist jij een enorme hoeveelheid potentiële deelnemers uit je hoge hoed te toveren. Ik weet niet wat ik zonder die mensen, en dus zonder jou, had moeten doen. Als ik ooit wat voor je terug kan doen...

Edith ter Braak Beste Edith, van jou heb ik de kunst van het clampen af mogen kijken. Het was altijd een genoegen met je te werken, ook daarna.

Ronald Stolk Beste Ronald, dank voor je heldere uiteenzetting over statistische aanpak en datapresentatie, vanuit het Juliuscentrum en (hooggeleerd) uit Groningen.

Ruud Bredewoud Beste Ruud, vanaf ons eerste telefoongesprek sprak je hartelijk, open, duidelijk en bevlogen met me over diabetes en het rijbewijs. Het werd me al snel duidelijk dat jij het beste met mensen met diabetes (en alle andere aanvragers van rijbewijzen) voor hebt. Op jouw aanwijzingen hebben we Hoofdstuk 8 tot een overzichtelijk en correct artikel kunnen maken.

Interne geneeskunde Academisch Ziekenhuis Utrecht Velen van u hebben zich, als arts, als polikliniekassistente of in een andere rol, ingezet voor het werven en selecteren van proefpersonen, en voor de logistiek rond de keuringen. Naast het grote belang hiervan voor het verloop van een onderzoek, heeft de goede sfeer, zeker ook op de poli Interne, er voor gezorgd dat ik me in het AZU (want zo blijf ik het gewoon noemen) enorm heb thuisgevoeld.

Zwaniek Homsma Lieve Zwaniek, ik heb pas later begrepen dat jij degene was die mijn sollicitatiebrief uit heeft gekozen voor het onderzoek dat ik hier eindelijk in dit proefschrift heb opgeschreven. Misschien herinner je je nog de verbijstering op mijn gezicht toen ik na het eerste gesprek met Willem wegliep, en nog niet helemaal begreep dat ik feitelijk naast een promotie ook een opleidingsplaats aangeboden had gekregen. Toen ik voor de feitelijke sollicitatie bij je kwam met een strak smoeltje had je me, op je beroemde stoeltje, al heel snel gerustgesteld, en wist ik dat het goed zat. Daarna alleen maar warmte en prettige gevoelens samen meegemaakt. Dat uiteindelijk het gouden team Erkelens/ Homsma uit elkaar ging heeft me pijn gedaan.

Annelies van den Burg Lieve Annelies, jij had de moeilijke taak om de leegte van het stoeltje bij Zwaniek op te vullen. Dat heb je op geheel eigen wijze gedaan, en ik heb me al snel helemaal bij je thuis gevoeld. Het was altijd een feest om bij je langs te komen, maar vooral om in de Ardennen het licht uit doen.

Bertie van Beelen Beste Bertie, je hebt de formele zaken rond mijn proefschrift geregeld en alle plooien glad gestreken. Alle lof.

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Harry Roos Beste Harry, vier verschillende bedrijven, 3 overnames, er is voor jou in de loop van de tijd het één en ander veranderd, maar ook veel hetzelfde gebleven. Jouw bevlogenheid om het leven van mensen met diabetes (en alleen zó mogen ze genoemd worden) aangenamer te maken, en beter te begrijpen, heb je overal ten toon gespreid. Ik denk dat we met dit onderzoek hetzelfde voor ogen hebben gehad. Jouw steun, op alle mogelijke manieren, is voor mij van groot belang geweest. Toen de lap-top was overleden,

wist jij de gegevens voor me van de harde schijf te halen. Onvergetelijk zijn de avonden met Jack (ik mocht John zeggen) en Jan-Willem in Philadelphia.

Maatschap Interne Geneeskunde Meander Medisch Centrum Tussen mijn onderzoek en het voltooien van dit proefschrift heb ik bij jullie het échte vak mogen leren. Stuk voor stuk uitgesproken persoonlijkheden heb ik denk ik van ieder van jullie dingen over kunnen nemen die mij maken tot de dokter die ik nu ben. Slechts één maal hebben jullie mij (letterlijk) de Zwarte Piet toegeschoven, en dat hebben we geweten...

Vasculaire Geneeskunde AMC: Harry Büller, John Kastelein, Marcel Levi, Saskia Middeldorp, Erik Stroes, Victor Gerdes en Pieter-Willem Kamphuisen Bij jullie kwam ik terecht in een warm bad. De geweldige, warme sfeer bij jullie is tegelijkertijd vertrouwd en inspirerend. De AMC-mentaliteit wordt door jullie met verve uitgedragen.

Frank Kristel Beste Frank, toen ik het echt nodig had, stond je voor me klaar met een laptop. Nogmaals hartelijk dank.

Hans en Jacqueline van den Boomen Lieve Hans en Jacqueline, het is toch een geweldig gevoel dat jullie me steunen. Ik hoop dat ik nog lang van jullie gezelligheid en vriendschap mag genieten, en dat ik ooit wat terug kan doen.

Cees de Jong Beste Cees, ingeschakeld door Hans heb je mij geholpen door het proces van het maken van een prachtig, smaakvol boek uit een stapeltje uitgeprinte artikelen. Jouw ervaring spreekt uit het representatieve eindresultaat. Eigenlijk ben je veel te goed voor het opmaken en uitgeven van een proefschrift, en daarom ik ben ik je des te dankbaarder dat je dit voor me hebt willen doen.

Diabetes Fonds Nederland Waar iedereen aangaf benieuwd te zijn naar de resultaten van het onderzoek beschreven in dit proefschrift, waren jullie als enige bereid dit ook financieel te ondersteunen. Hartelijk dank voor jullie vertrouwen

Alle deelnemers aan DADS Aan u allen ben ik veel dank verschuldigd. Want wat is een onderzoek zonder deelnemers? U heeft zich moedig opgegeven en heeft alles wat bij het onderzoek hoort ondergaan, zelfs al was dat niet altijd even makkelijk. Onder u een deel van mijn (schoon-)familie. Hartelijk dank dat jullie je voor mij opgeofferd hebben (keuring, 's morgens vroeg aanwezig zijn, infusen...). Ik hoop dat dit onderzoek ertoe bij zal dragen dat u door de wetgevers op een zo eerlijk mogelijke wijze benaderd zult worden.

Velen hebben in meer of mindere mate een bijdrage geleverd aan de totstandkoming van dit proefschrift. Ook degenen die niet op deze pagina's vermeld zijn (vergeef het me) ben ik veel dank verschuldigd.

Familie Mijn diepste dank en waardering gaat uit naar jullie, mijn ouders, Jeanette en de jongens, die mij onvoorwaardelijk hebben gesteund. Joop, van jongs af aan heb je mij gesteund en gestimuleerd en ben je als vader, als mens en als dokter een voorbeeld voor me geweest. Door jouw betrokkenheid en enthousiasme hebben we samen vele fijne medische discussies gevoerd. Meer toewijding had ik me niet kunnen wensen. Dank jullie allemaal.

Alexander Stork, september 2006