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Critically ill patients with haematological malignancies

Addition of liraglutide to insulin in type 2 diabetes

The economic burden of diabetes in the Netherlands

Tularemia
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Editorial office
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Department of Internal Medicine
’s-Gravendijkwal 230
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The Netherlands
Tel.: +31 (0)10-703 39 54
Fax: +31 (0)10-703 32 68
E-mail: p.l.a.vandaele@erasmusmc.nl
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Health promotion and disease prevention can substantially reduce the total economic burden of diabetes in the Netherlands

J.A.M.J.L. Janssen
Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands, email: j.a.m.j.l.janssen@erasmusmc.nl

Increased healthcare expenditures are not a guarantee for better overall health of a population. Diabetes, especially type 2, is responsible for substantial healthcare expenditures in the US, the Netherlands and many other countries in Europe, but despite increasing economic costs the prevalence of diabetes and its complications continues to rise.1,4 Overall the US spends per capita on healthcare almost double the average of other Organisation Economic Co-operation and Development (OECD) countries.1,3 Nevertheless, despite these higher economic costs, the Americans are not gaining benefits that commensurate with these higher expenditures: dozens of countries today even boast superior life expectancy compared with the US,3 showing that the healthcare expenditures as such do not go hand in hand with better health.

In this issue of the Netherlands Journal of Medicine, Peters et al. present a literature review which aimed to determine the current total economic burden of diabetes and its complications in the Netherlands.4 They found that the total costs of diabetes were quite similar to those previously reported in the UK by Hex et al.3 Peters et al. further came to the conclusion that diabetes and especially its complications pose a substantial burden on the Netherlands and predicted that this burden will increase further in the near future due to changing demographics and lifestyle. They suggested that a further rise in costs is unavoidable and cannot be halted in the near future.

One of the major limitations of descriptive cost analyses, such as those conducted by Peters et al., is that they do not provide an indication of the value obtained for the money spent. The chronic nature of diabetes and the high incidence of complications are the main reasons behind the high costs involved.1 Complications related to diabetes account for a substantial proportion of the direct health costs.1 Therefore, with increasing prevalence of diabetes the costs of treating complications will grow if current care regimes and strategies are maintained without any changes.3

Because the risk of developing diabetes and its complications further increases with age, the ageing population is expected to drive a substantial increase in the incidence of diabetes even if other risk factors remain unchanged.1 As the total costs are proportional to the size of the affected population, stemming the rise in costs for diabetes will only be possible by successful diabetes prevention.6 Thus primary prevention may provide the greatest potential to reduce costs.

In this respect type 2 diabetes can function as a good model for management of other chronic diseases.7 Modern obesogenic environments, with the combination of unhealthy diet and physical inactivity, have serious implications for type 2 diabetes, and many other chronic diseases. However, it has been shown that type 2 diabetes and its complications, especially for people at high risk, can be delayed or even avoided by prevention programs.8-10 Evidence from large trials in Finland as well as real-world prevention programs have identified that lifestyle interventions can prevent or delay the onset of type 2 diabetes in people at high risk.8-10 Specifically the risk of developing type 2 diabetes can be reduced over a 3-5 year period for people with impaired fasting glucose tolerance by intensive lifestyle modification programs (58%) and pharmacological interventions (31%).10

Ideally, prevention programs should combine broad population-based primary prevention strategies for other chronic diseases, such as cardiovascular disease and cancer, while simultaneously targeting people at high risk of developing diabetes.11,12 In addition, research has also shown the benefits of an integrated approach in the case of subjects who have developed type 2 diabetes: intensifying treatment including tight control of multiple risk factors as high blood glucose, blood pressure and cholesterol have been found to significantly reduce the risk of death from...
cardiovascular diseases and the development of end-stage renal disease.\textsuperscript{7,8} Health promotion and the prevention of chronic diseases often has a low priority and as a consequence receives too small a share of the overall healthcare budget. The focus is often mainly on care for people who have already developed a disease.\textsuperscript{7,11} In their paper Peters et al. also do not present data about the costs of prevention of diabetes in the Netherlands.\textsuperscript{4}

It is time for a treatment paradigm shift in light of the proven, evidence-based, value of early intensive treatment in preventing diabetes and its chronic diabetes complications.\textsuperscript{7,13} What is needed is the introduction of a comprehensive and integrated patient-centred approach that focuses on health promotion and starting early interventions to prevent the development of diabetes and its complications.\textsuperscript{7,13} Such an approach is relatively inexpensive to implement and highly cost-effective compared with the actual costs of treating the complications of diabetes.

\textbf{REFERENCES}

The management of critically ill patients with haematological malignancies

N. Kusadasi¹,²*, M.C.A. Müller³, D.J. van Westerloo⁴, A.E.C. Broers⁵, M.G.E.C. Hilkens⁶, N.M.A. Blijlevens⁷ on behalf of the HEMA-ICU study group

¹Department of Intensive Care Medicine, Erasmus Medical Center, Rotterdam, the Netherlands, ²Department of Intensive Care Medicine, Utrecht University Medical Center, the Netherlands, ³Department of Intensive Care Medicine, Academic Medical Center, Amsterdam, the Netherlands, ⁴Department of Intensive Care Medicine, Leiden University Medical Center, Leiden, the Netherlands, ⁵Department of Haematology, Erasmus Medical Center Rotterdam, the Netherlands, ⁶Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, the Netherlands, ⁷Department of Haematology, Radboud University Medical Center, the Netherlands, *corresponding author: n.kusadasi@umcutrecht.nl

ABSTRACT

The management of critically ill patients with haematological malignancy (HM) still shows inter- and intra-regional differences. Our objective in this updated review was to address the evidence supporting the potential treatment options, based on multidisciplinary processes, of critically ill patients with HM. A stepwise approach to the critical care pathway of this patient population from the triage to ICU admission to ICU discharge was chosen to emphasise certain key findings. Our main focus relied on significant issues of decision-making in daily clinical routine. The plethora of studies shifted the pragmatic treatment policy into an evidence-based approach. The transfer of a patient with HM from the haematology ward to the ICU and vice versa should be based on a well-defined clinical care process in which the haematologists and intensivists are in close collaboration and direct communication. A protocolised clinical approach to treat a critically ill patient with HM seems helpful to optimise patient-oriented care and patient safety.

KEYWORDS

Critically ill, haematological malignancies, outcome, prognostic factors, systemic review

INTRODUCTION

In the last decades, there has been increasing evidence regarding the improved survival of patients with haematological malignancies (HM) admitted to the intensive care unit (ICU). The management of the critically ill patient with HM has shifted from no admission to a short ICU admission period. Clinicians often follow a pragmatic policy, as described by several groups.¹⁻⁴ Patients undergoing first-line immunotherapy and chemotherapy regimens and those with low-grade malignancies and partial/complete remissions receive full treatment. Patients for whom there is uncertainty about the benefit of ICU support, in terms of survival, are admitted and receive full ICU treatment. In this last group, reassessment after 3 to 5 days is often desirable, and if there is no improvement or a deterioration, the treatment can then be adjusted. For patients who are not undergoing treatment modalities for urgent HM, a highly restricted to no ICU admission policy is followed.

However, there are still considerable inter- and intra-regional differences in the ICU admission policy for the patient with HM.⁵⁻⁸ These discrepancies in admission policy formed the basis for the development of a Dutch guideline discussing the pathways of care for critically ill patients with HM. This guideline has been approved by the Dutch Society of Intensive Care and will shortly be approved by the Dutch Society of Haematology. A concise and precise summary of the guideline has recently been published.⁷ Because new evidence was published recently we decided to review this for a more general public of....
internists. The level of evidence of these studies was similar to that used in the guideline and showed mainly an evidence level of B for methodological quality according to CBO / EBRO guidelines (www.cbo.nl). We refer the reader to the guideline for a detailed description of the level of evidence-based recommendations. The existing knowledge supports the substantial contribution of a multidisciplinary approach in the treatment of critically ill patients with HM. Haematologists and intensivists play a central role in this. Notably, most studies have a heterogeneous patient population and a descriptive study design, either retrospective or prospective.

In this review we performed a stepwise approach to the critical care pathway of this patient population. The triage from consultation to ICU admission to ICU discharge was chosen to emphasise certain key findings. Our main focus relied on significant issues of decision-making in daily clinical routine during ICU admission. The factors influencing this triad will be addressed based on evidence summarised in consecutive order in the subheadings below. In doing so, we aim to optimise the collaboration between the haematologists and intensivists. This in turn might improve the evidence-based decision-making in daily clinical routine of critically ill patient with HM.

ICU ADMISSION AND OUTCOME OF PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

The prognosis of patients with HM has improved in recent decades through chemotherapy dose adjustments, the prevention of nosocomial infections and the introduction of new antiviral and antifungal drugs. The survival of vitally threatened patients has improved with early sepsis recognition and intervention and lung protective mechanical ventilation. There is increasing evidence about improved survival of patients with acute or chronic and myeloid or lymphoid derived HM admitted to the ICU.8–11 There are several studies regarding the outcome of patients with acute myeloid leukaemia admitted to the ICU. Just recently, ICU and hospital survival of patients with diffuse large B-cell lymphoma was described as 75.7% and 70.3%, respectively.12 Different clinical emergencies related to HM necessitate adjusted ICU support, such as successful first-induction chemotherapy in the ICU after pre-treatment with oral hydroxyurea for patients with HM-related leukostasis.13–14 The mortality has been shown to be lower for patients pre-treated with hydroxyurea (34% vs. 19%, p = 0.047).14

The post-ICU long-term prognosis seemed to be primarily influenced by the successful continuation of haematological treatment regimes. Patients with allogeneic stem cell transplantation (SCT) receiving reduced intensity conditioning seemed to have better 1- and 3-year post-ICU survival than patients undergoing myeloablative conditioning, as shown by Townsend and colleagues. In that article, however, ICU admissions within 5 years after SCT were included indicating different ICU admission reasons at different time points after SCT. Also the long-term health-related quality of life (HRQoL) of patients with HM seemed to be similar to that of patients who were not admitted to the ICU. These data indicate that the assumption that ICU admission has a negative impact on HRQoL is unfounded and that the decision to admit a patient to the ICU should not depend on this assumption. If the HM is refractory with a poor prognosis, transfer to an ICU is highly undesirable. The same applies when the patient or family has expressed the wish not to undergo life-sustaining treatments.1,17–19 For an objective approach to a clinical problem, some have divided patients with HM into subgroups. These subgroups, as proposed by Bird et al., can help to decide whether admitting a patient with HM to the ICU could positively influence survival. In this study poor predictors were defined as relapsed or failed treatment, disease unresponsive to therapy, and/or successive failure of > 2 organ systems.

In conclusion, available evidence shows that the survival of HM patients has significantly improved in recent years. Additionally, the quality of life after ICU admission seemed comparable with patients without HM. There is ample evidence in favour of a broad ICU admission policy for patients with HM.

TIMING OF ICU ADMISSION AND OUTCOME OF PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

The increased delay between the onset of the first symptoms to ICU admission of a patient with HM has been shown to be an independent predictor of mortality.20 Several researchers have described the importance of so-called early warning scores and the early involvement of ICU outreach teams and medical emergency teams in the early ICU admission of patients with HM.21–24 The duration of less than 24 hours from the onset of the first symptoms to ICU admission was associated with improved survival.21 Lengliné et al. emphasised the importance of early ICU admission (defined as admission at presentation of acute symptoms and before induction chemotherapy). These authors show that late ICU admission (defined as admission from the haematology ward) resulted in an increase in the use of mechanical ventilation (60% vs. 33%) and use of vasopressors (60% vs. 16%), longer ICU
stay (9 [6-25] vs. 5 [2-9] days) and decreased ICU survival (65% vs. 79%) compared with early ICU admission. In a prospective study of patients with cancer (84% of the patients had HM), Mokart et al. showed that a delay of more than 2 days from the start of respiratory symptoms to ICU admission was associated with higher 28-day ICU mortality. These authors state that early ICU admission for patients with malignancy and acute respiratory failure could lead to better survival.

Altogether, the majority of the publications emphasise the importance of early ICU admission in critically ill patients with HM. However, the term ‘early’ is not clearly defined, making it difficult to properly define the justified timing of admission in daily routine. A very limited number of studies used as definition either the arrival at the hospital or 1 to 4 days from the onset of symptoms to the ICU admission. It can be concluded that delayed ICU admission is associated with increased mortality. Based on expert opinion, admission should be as early as possible, ideally before development of multiple organ failure.

REPRODUCTIVE SUPPORT AND OUTCOME OF PATIENTS WITH HAEMATOLOGICAL MALIGNANCES

Many studies indicate that early mechanical ventilation can favourably impact the prognosis. In a recent retrospective study, the feasibility of high-flow nasal cannula oxygen (HFNO) therapy for acute respiratory failure in patients with HM was evaluated. Of the 45 patients, 33% successfully recovered, and 67% required invasive mechanical ventilation due to failure of this treatment. In addition, in immunocompromised patients (approximately 60% HM) with hypoxaemic acute respiratory failure, support with HFNO improved neither mechanical ventilatory assistance nor patient comfort nor survival rates compared with oxygen delivered via a Venturi mask. In contrast, recent studies indicate that immunocompromised patients with hypoxaemic acute respiratory failure treated with non-invasive ventilation (NIV) might be associated with an increased risk of intubation and mortality compared with those treated with HFNO.

Others emphasise the importance of NIV at an early stage, indicating that it results in a significant decrease in mortality. Although non-invasive modalities can be seen as an interesting alternative for invasive mechanical ventilation in patients with acute respiratory failure, others stress the high percentage of NIV failure in these patients. An Italian retrospective study compared NIV with invasive mechanical ventilation. In this study, 21% of the patients received NIV at ICU admission and 46% of these patients later required invasive mechanical ventilation. Also a Spanish prospective multicentre study of 450 patients with HM shows that 60% of patients initially treated with NIV later required invasive mechanical ventilation. Mortality in this latter group was 80%. The odds ratio of death was 5.74 for NIV failure and 1.13 for invasive mechanical ventilation at ICU admission. In a randomised study, Wermke et al. showed no advantage of NIV on the study endpoints of ICU admission frequency, need for endotracheal intubation and survival. These authors and others described the severity of illness and the presence of adult respiratory distress syndrome as risk factors for this NIV failure. They also emphasised that this subgroup of patients is precisely the one for which early endotracheal intubation should be considered. In conclusion, a few studies indicate that early non-invasive support (NIV and/or HFNO) may favourably influence the prognosis in some subpopulation of patients. Others emphasise the importance of early endotracheal intubation in patients with a high probability of NIV failure.

PROGNOSTIC FACTORS OF CRITICALLY ILL PATIENTS WITH HM

A broad range of haematological and ICU prognostic factors have been evaluated during the ICU admission of patients with HM. The evaluated ICU severity of illness scores were the Acute and Chronic Health Evaluation (APACHE) II/III/IV, Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Assessment (SOFA) scores. High APACHE IV and SOFA scores have been shown to be related to ICU mortality. Others emphasised ICU support-related factors as being significant for mortality rates. In this perspective, the use of mechanical ventilation, vasopressors and haemodialysis were associated with 60.5%, 57.5% and 36.8% mortality, respectively.

There is also plethora of evidence focussing on the impact of haematological factors on ICU mortality. Here we want to briefly focus on neutropenia, Eastern Cooperative Oncology Group score (ECOG, also known as the WHO performance score or Zubrod score) and allogeneic SCT patients in consecutive order. In a retrospective study the combination of a positive blood culture and neutropenia seemed to be associated with increased 28-day mortality suggesting that this could be of additional value when assessing mortality risk in this patient group. In contrast, in a recent meta-analysis, there was no significant impact of neutropenia on mortality (risk difference of mortality, 9%; 95% CI -1.5 to +3.3) in critically ill cancer patients nor was neutropenia of importance in the Dutch NICE cohort. In addition, an ECOG score > 2 at ICU discharge
In this perspective, Soares et al. summarised the decision-making process of critically ill haematological and oncological patients. In this view, a multidisciplinary panel of experts, brought together by the French Intensive Care Society, summarised their recommendations about the management of this specific patient population. In short, they advocate additional studies since most of the provided recommendations were obtained from low levels of evidence. We want to focus on the additional role of a pharmacist in the multidisciplinary approach of the treatment of critically ill patients with HM. In this perspective, Soares et al. showed that the presence of clinical pharmacists in

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Additionally, the implementation of oncologists and intensivists for care planning (OR 0.69; 95% CI 0.52 to 0.91) were associated with lower mortality. They also showed that the implementation of protocols (OR 1.52; 95% CI 1.11 to 2.07) and meetings between oncologists and intensivists (OR, 4.70; 95% CI, 1.15 to 19.22) were independently associated with more efficient resource use. In addition, Coutsouvelis et al. described that medication information transfer by a pharmacist at ICU admission ensured that the medication was prescribed correctly and at the right times. This may improve both continuity of care and patient safety. A recent multivariate analysis showed that a low voriconazole level was an independent predictor of therapy failure. In addition, Blackburn and colleagues showed recently that an increased volume of distribution of aminoglycosides (amikacin and tobramycin) was identified in critically ill patients with HM, and that current dosing yielded a suboptimal concentration (peak) in the majority of patients. Taken together, these studies indicate the importance of drug monitoring and the crucial role of the pharmacist in the critical care pathway. Almost all of the published articles emphasise the importance of beginning physical therapy as early as possible, ideally during the ICU admission.

**Volume-outcome relationship in critically ill patients with HM**

In a retrospective study of 1753 haematological patients with acute respiratory failure, LeCuyer et al. described that the mortality in ICUs with a high volume (> 30 patients with HM admitted to the ICU each year) was lower than that of ICUs with a low volume (< 12 patients with HM admitted to the ICU each year). However, this finding was only clear after adjusting for prognostic factors for ICU mortality and the use of propensity scores. This volume effect was not observed in a recently published Dutch National Intensive Care Evaluation (NICE) database analysis. Albeit, an increasing number of articles emphasise the importance of centralisation for severe sepsis treatment. These studies show an inverse relationship between the number of severe sepsis admissions and hospital mortality. Gaieski et al. showed that the hospital mortality of severe sepsis patients with one organ failure in low-volume ICUs (defined as < 50 cases admitted to the ICU each year) was 18.9%, while the hospital mortality in high-volume ICUs (defined as > 500 cases admitted to the ICU each year) was 10.4%. Similar differences were also found in cases of severe sepsis with multiple organ failure. Although these data cannot directly be extrapolated for ICU patients with HM, they do suggest the importance of treatment in centres with haematological expertise.

**Post-ICU prognosis of patients with HM**

There are limited data about the post-ICU period for patients with HM. The available literature mainly focuses on the long-term prognosis and quality of life, as described in a previous section of this review. We emphasise the importance of the consultant intensive care nurse (CIN) and medical intervention team (MET) during the early post-ICU period. Endacott et al. found that the CIN can play an important role in preventing complications after ICU discharge. Green and Edmonds found that ICU readmissions decreased from 2.3% to 0.5% within 5 years after the implementation of a CIN. In another study, the presence of a CIN resulted in the early detection of clinical deterioration and the prevention of complications such as ICU readmission. Additionally, the implementation of a MET seemed to improve hospital survival and reduced the number of ICU readmissions. The implementation of a CIN and/or a MET may play an important role in improving the quality of care for patients with HM after ICU discharge. The designation of a responsible group of nurses in both departments can optimise continuity of care and the exchange of expertise and low-threshold consultation. Although there are no data on this matter, it is also important to discuss the ICU readmission policy and any treatment restrictions upon discharge. It appears that haematological ICU patients need more time to physically rehabilitate than non-haematological ICU patients, often longer than 1.5 years. This could be explained in part by the combination of underlying disease, haematological treatment and the impact of an ICU admission on physical well-being. In turn, these physical limitations seem to affect patients’ experienced quality of life in the long-term. Because of this, several authors indicate the importance of beginning physical rehabilitation as early as possible, ideally during the ICU admission.

**Conclusion**

The prognosis of critically ill patients with HM has improved in the last decade. The plethora of studies shifted the pragmatic treatment policy into a more evidence-based approach. The transfer of a patient with HM from the
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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A cost-controlling treatment strategy of adding liraglutide to insulin in type 2 diabetes

H.M. de Wit*, G.M.M. Vervoort, B.E. de Galan, C.J. Tack

Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands, *corresponding author: hmdewit@gmail.com

ABSTRACT

Background: Addition of the GLP-1 receptor agonist liraglutide to insulin can reverse insulin-associated weight gain, improve HbA1c and decrease the need for insulin, but is expensive. From a cost perspective, such treatment should be discontinued when it is clear that treatment targets will not be achieved. Our aim was to find the best cost-controlling treatment strategy: the shortest possible trial period needed to discriminate successfully treated patients from those failing to achieve predefined targets of treatment success.

Methods: We used data from the ‘Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes’ (ELEGANT) trial, comparing additional liraglutide (n = 47) and standard insulin therapy (n = 24) during 26 weeks, to calculate the costs associated with different trial periods. Treatment success after 26 weeks was defined by having achieved ≥ 2 of the following: ≥ 4% weight loss, HbA1c ≤ 53 mmol/mol (7%), and/or discontinuation of insulin.

Results: The additional direct costs of adding liraglutide for 26 weeks were € 699 per patient, or € 137 per 1 kg weight loss, compared with standard therapy. The best cost-controlling treatment strategy (identifying 21 of 23 responders, treating four non-responders) was to continue treatment in patients showing ≥ 3% weight loss or ≥ 60% decrease in insulin dose at 8 weeks, with a total cost of € 246 for this trial period, saving € 453 in case of early discontinuation.

Conclusion: An 8-week trial period of adding liraglutide to insulin in patients with insulin-associated weight gain is an effective cost-controlling treatment strategy if the liraglutide is discontinued in patients not showing an early response regarding weight loss or insulin reduction.

KEYWORDS

Cost-management, insulin therapy, liraglutide, type 2 diabetes, weight gain
be further reduced by early selection of patients with a positive response, allowing timely discontinuation in non-responders. The aim of the present study was to determine the best cost-controlling treatment strategy for additional GLP-1 receptor agonist treatment in patients with type 2 diabetes and pronounced insulin-associated weight gain: the shortest possible trial period while yielding the highest number of effectively treated patients.

MATERIALS AND METHODS

A simulation model was developed using data from the ELEGANT randomised controlled trial, which was conducted in the Netherlands between February 2012 and April 2014. The methods of this trial have been described previously. Briefly, patients with type 2 diabetes who had shown pronounced (>4% of body weight) weight gain between 3 and 16 months after the initiation of insulin therapy were randomised either to addition of liraglutide (1.2 or 1.8 mg) to insulin therapy or to continuation of standard insulin therapy for 26 weeks. The study had a waiting-list design so that patients who initially continued insulin therapy from 0-26 weeks, which was uptitrated when necessary to achieve treatment targets, were also offered liraglutide treatment from 26-52 weeks. As clinical effects of liraglutide treatment were similar for both groups of patients, we pooled the 26-week data on liraglutide-insulin combination therapy from the entire study population (n = 47). These data were compared with the 26-week data from the group of patients initially continued insulin therapy from 0-26 weeks, which was uptitrated when necessary to achieve treatment targets, and used for the simulation model to calculate 8, 12, 16 and 26-week health outcomes.

Study protocol

After inclusion, participants in the ELEGANT trial were evaluated every 4-6 weeks (study visits at 0, 4, 8, 12, 16, 20 and 26 weeks) for adverse events, hypoglycaemia, body weight and insulin dose, and every 8 weeks for HbA1c (determined at 0, 8, 16 and 26 weeks). Liraglutide was initiated at 0.6 mg/day and increased over two weeks to 1.8 mg/day. When adverse events occurred, participants were allowed to return to the 1.2 mg dose. When liraglutide was started, the total insulin dose was decreased by 20% to avoid hypoglycaemia. Participants were instructed to perform daily (4-point) capillary blood glucose profiles during the first 3 weeks after the start of liraglutide, and twice weekly thereafter. Patients who continued standard insulin treatment were instructed to perform capillary blood glucose profiles at their own discretion, but at least once weekly. At every study visit, the insulin dose was adjusted aiming for a fasting glucose target of 4.0-6.5 mmol/l. The dose of oral glucose-lowering agents (metformin and sulphonylurea) remained unchanged unless hypoglycaemia persisted after the discontinuation of insulin.

Simulation model structure

The model was developed as a decision tree that compared health outcomes within a treatment period of 26 weeks consisting of: 1) continuation and uptitration of standard insulin therapy, or 2) liraglutide 1.2-1.8 mg once daily added to standard insulin therapy (figure 1). The second treatment strategy could result in three different scenarios: a) adverse events, prompting the discontinuation of liraglutide; b) ineffectiveness of the therapy (not meeting treatment targets), which should also lead to discontinuation of liraglutide; or c) effectiveness of the therapy, justifying the continuation of liraglutide from a clinical point of view. Effectiveness was defined as achieving at least two of the following treatment targets after 26 weeks of liraglutide treatment: 1) ≥4% weight loss, and/or 2) HbA1c ≤53 mmol/mol (7%), and/or 3) discontinuation of insulin therapy without adverse events. Key events and changes in therapy over the 26-week treatment period included changes in insulin dose, uptitration of liraglutide to the maximum tolerable dose (1.2 or 1.8 mg), treatment discontinuation due to adverse events (trial-based: at 4 weeks and within 12 weeks), and failure to achieve treatment targets regarding weight loss, HbA1c and discontinuation of insulin therapy.

Model inputs

Model inputs were derived from the ELEGANT trial; medical expenditure inputs were derived from pharmacy costs (Zorginstituut Nederland), as explained below. Costs were defined from a health care perspective, societal costs were excluded.

Effectiveness of liraglutide and insulin use

Effectiveness inputs and patient flow including drop-out rates for the use of liraglutide and/or insulin were derived from the ELEGANT trial (figure 1 and table 1). Treatment efficacy was evaluated based on body weight, HbA1c, and insulin dose.

TREATMENT COSTS

Direct medical expenditure, consisting of medication-related costs (insulin, liraglutide, needles, and test strips needed to perform daily self-measured capillary blood glucose profiles), was derived from pharmacy costs (Zorginstituut Nederland) and evaluated at 8, 12, 16 and 26 weeks.

Nine of 47 (~1/5) patients were on a liraglutide dose of 1.2 mg, so that the average liraglutide dose for all patients was 1.7 mg (at ~€ 2.83 per mg). For insulin, we calculated the average costs per unit of insulin, based on the insulin
regimens that were used by the trial participants: 54% used basal insulin only (€ 0.037 per unit); 34% were on basal-bolus regimens (€ 0.033 per unit); and 12% were on biphasic insulin (€ 0.027 per unit). This translated into € 0.034 per unit of insulin. The change in insulin dose (units per day) for each participant and treatment group was derived from the ELEGANT trial and included the 20% decrease in insulin dose when liraglutide was started. We assumed a 100% adherence for both liraglutide and insulin, while on treatment. We assumed that injection needle costs increased with one additional needle (€ 0.20 per needle) per day after the start of liraglutide, and were reduced by two needles per day after the discontinuation of insulin. Patients used disposable test strips for performing self-measured capillary blood glucose profiles (€ 0.50 per strip). Following the study protocol, 28 strips per week were used in the first 3 weeks after the start of liraglutide to perform daily (4-point) capillary blood glucose profiles, and eight strips per week thereafter. We assumed that patients continuing standard insulin therapy used four strips per week and that patients who could discontinue insulin therapy no longer performed blood glucose profiles. We did not model costs related to the use of metformin and sulfonylurea. Also, we did not include the costs associated with a visit to the doctor or laboratory in the model, as these were the same for patients in both groups.

Treatment discontinuation and adverse effects
In the ELEGANT trial, 4 of 47 (8.3%) patients discontinued liraglutide due to adverse effects. We assumed that two patients stopping liraglutide within 4 weeks incurred drug costs for 28 days, and those stopping later (within 8 and 9 weeks) incurred drug costs for 12 weeks of treatment, but not with any additional costs. We also assumed return to baseline levels of insulin dose, HbA1c, and body weight in patients who discontinued therapy. Two of 24 patients (8.3%) who were initially assigned continuation of standard insulin treatment withdrew consent after 1 and 10 weeks of follow-up, respectively, both of whom are included in the present analysis. We did not take into account costs related to adverse effects. Although particularly gastrointestinal adverse effects occurred more frequently with liraglutide than with standard insulin therapy (52.8% versus 8.3%), they were mostly mild-to-moderate in severity, typically resolved after 4-8 weeks, and did not lead to hospital admission, increased medication costs or unscheduled outpatient visits. As hypoglycaemia rates did not differ between the two groups,10-12 we did not incorporate hypoglycaemia into our model either.

Model outcomes
The simulation model was used to answer the following questions. First, the total costs of adding liraglutide to insulin for 26 weeks were calculated, on the basis of intention to treat. Then, we calculated costs associated with a trial period of 8, 12 or 16 weeks of adding liraglutide to existing insulin therapy, as compared with continuation and uptitration of standard insulin therapy. Second, the incremental costs (ICER = incremental cost-effectiveness ratio) per 1 kg weight loss and per 1% decrease in HbA1c were calculated. Third, several thresholds regarding weight loss (in %), change in HbA1c, and reduction in insulin dose (in %) at 8, 12 and 16 weeks were explored, to predict if a patient would meet the predefined treatment targets after 26 weeks of liraglutide treatment. We assumed that patients who would not meet these targets discontinued liraglutide treatment. These calculations were performed to find the shortest possible trial period that would yield the highest number of successfully treated patients and the lowest number of patients not meeting treatment success, translating into the lowest costs per successfully treated patient.

Statistical analyses
All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, NY). Missing data were imputed according to last-observation-carried-forward. As both groups were comparable at baseline regarding insulin regimen (both 2.1 insulin injections per day) and insulin dose (55.6 ± 34.9 units/day for liraglutide arm, 50.0 ± 32.9 units/day for standard insulin therapy, p = 0.51), we used raw data to calculate treatment costs, not using a linear mixed model. Results for subgroups were tested for normal distribution and are displayed as mean ± standard error.

RESULTS

Figure 1 represents the simulation model, including the number of participants in the ELEGANT trial assigned to a certain treatment, dropping out, and achieving the predefined treatment targets of ≥ 4% weight loss, HbA1c ≤ 53 mmol/mol (7%) and discontinuation of insulin after 26 weeks of treatment. In total, 23 out of 47 patients achieved at least two of these treatment targets.

Costs of additional liraglutide treatment
The additional costs of adding liraglutide to insulin treatment in the ELEGANT trial amounted to € 246 per patient after 8 weeks of treatment, and € 699 per patient after the full 26 weeks of treatment, as compared with continuation and uptitration of standard insulin therapy (table 1). As liraglutide reduced body weight by -4.3 ± 0.6 kg, the ICER for a 1 kg reduction in body weight was € 137; the ICER for a 1% decrease in HbA1c was € 999 (table 1). These costs are spent in all patients, including non-responders.

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Early predictors of treatment success at 26 weeks

Figure 2 represents changes in body weight, HbA1c or insulin dose at 8, 12 and 16 weeks for responders (patients meeting at least two of the predefined treatment targets at 26 weeks) and non-responders. An early weight loss of 2.5-3% was a strong indicator of long-term treatment success, whereas a change in HbA1c did not differentiate between responders and non-responders, neither at 8 nor at 16 weeks. The best treatment strategy for controlling costs, using weight change only, was to discontinue liraglutide after a treatment period of 8 weeks in patients showing less than 3% weight loss. This strategy would erroneously include four non-responders and exclude five responders not yet identified as such. At the 8-week time point, three of these five responders showed a more than 60% reduction in insulin dose. Consequently, a strategy based on a mixed criterion of either ≥ 3% weight loss or ≥ 60% decrease in insulin dose at 8 weeks would be more cost-controlling, correctly identifying 21 of 23 responders, whilst four non-responders would be treated ‘erroneously’ until week 26. Using such an 8-week trial period as a go/no-go decision point would correspond to a sensitivity of 91%, specificity of 83%, positive predictive value of 84% and negative predictive value of 91%.

Treatment costs for the best cost-controlling treatment strategy

Application of ≥ 3% weight loss or ≥ 60% reduction in insulin dose at 8 weeks as early response criteria, with discontinuation of liraglutide in those not meeting one of these targets, would decrease additional treatment costs for the whole group of 47 patients from € 32,858 to € 22,888 for a period of 26 weeks, saving € 9970, or € 453 per non-responding patient. As costs for the 8-week trial period amount to € 246 per non-responder, total costs per effectively treated patient would decrease from € 1429 to € 1079 for the first 26 weeks with this strategy. After 26 weeks, the additional costs for liraglutide treatment are € 957 for 6 months, assuming that the insulin dose will not change.

DISCUSSION

The present analysis of the ELEGANT trial shows that the addition of liraglutide to insulin treatment is associated with an additional cost of ~€ 700 for 26 weeks, or ~€ 140 per 1 kg weight loss, but that the total costs per effectively treated patient would decrease by € 350 for the first 4 weeks.
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Figure 2. Change in body weight (A), HbA1c (B) and insulin dose (C) for responders (white squares) versus non-responders (black circles) at various early time points. Treatment response was determined on the basis of meeting at least two of the following treatment targets at 26 weeks: ≥ 4% weight loss, and/or HbA1c ≤ 53 mmol/mol (7%), and/or discontinuation of insulin therapy. Horizontal bars represent optimal cut-off points for identifying early treatment response including as many responders as possible whilst few non-responders are included.
### Table 1. Costs and outcomes per patient for a short-term treatment period of adding liraglutide versus continuation of standard insulin therapy

<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>16 weeks</th>
<th>(26 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin (€ 0.034 per unit)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide + insulin</td>
<td>– 1147 ± 144U</td>
<td>– 1862 ± 239U</td>
<td>– 2535 ± 332U</td>
<td>– 4604 ± 609U</td>
</tr>
<tr>
<td>Standard (insulin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>29 ± 29U</td>
<td>102 ± 57U</td>
<td>224 ± 98U</td>
<td>880 ± 516U</td>
</tr>
<tr>
<td><strong>Liraglutide (€ 2.83 per mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide + insulin</td>
<td>81.6 ± 2.0mg</td>
<td>127.0 ± 3.7mg</td>
<td>170.6 ± 5.6mg</td>
<td>279.6 ± 10.7mg</td>
</tr>
<tr>
<td>Standard insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Needles (€ 0.20 per needle)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide + insulin</td>
<td>51 ± 2</td>
<td>73 ± 4</td>
<td>92 ± 7</td>
<td>131 ± 14</td>
</tr>
<tr>
<td>Standard insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Test strips (€ 0.50 per strip)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide + insulin</td>
<td>121 ± 1</td>
<td>150 ± 3</td>
<td>176 ± 4</td>
<td>239 ± 8</td>
</tr>
<tr>
<td>Standard insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>32 ± 0</td>
<td>48 ± 0</td>
<td>64 ± 0</td>
<td>104 ± 0</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide + insulin</td>
<td>€ 262.92 ± 8.00</td>
<td>€ 385.85 ± 11.07</td>
<td>€ 503.41 ± 18.66</td>
<td>€ 781.03 ± 34.13</td>
</tr>
<tr>
<td>Standard insulin</td>
<td>€ 16.98 ± 1.00</td>
<td>€ 27.46 ± 1.93</td>
<td>€ 39.63 ± 3.33</td>
<td>€ 81.93 ± 10.75</td>
</tr>
<tr>
<td>Difference</td>
<td>€ 245.93 ± 7.00</td>
<td>€ 358.38 ± 11.14</td>
<td>€ 463.75 ± 15.33</td>
<td>€ 609.10 ± 23.38</td>
</tr>
<tr>
<td><strong>Body weight change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide + insulin</td>
<td>– 3.0 ± 0.4kg</td>
<td>– 3.4 ± 0.5kg</td>
<td>– 3.9 ± 0.5kg</td>
<td>– 4.3 ± 0.6kg</td>
</tr>
<tr>
<td>Standard insulin</td>
<td>0.2 ± 0.3kg</td>
<td>0.4 ± 0.3kg</td>
<td>0.6 ± 0.4kg</td>
<td>0.8 ± 0.5kg</td>
</tr>
<tr>
<td>Incremental costs (per 1 kg weight loss)</td>
<td>€ 76.85</td>
<td>€ 94.31</td>
<td>€ 103.06</td>
<td>€ 137.08</td>
</tr>
<tr>
<td><strong>HbA1c change (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide + insulin</td>
<td>– 0.8 ± 0.1%</td>
<td>NA</td>
<td>– 0.9 ± 0.1%</td>
<td>– 0.7 ± 0.1%</td>
</tr>
<tr>
<td>Standard insulin</td>
<td>± 0.1%</td>
<td>NA</td>
<td>± 0.1%</td>
<td>0.0 ± 0.1%</td>
</tr>
<tr>
<td>Incremental costs (per 1% decrease in HbA1c)</td>
<td>€ 307.41</td>
<td>NA</td>
<td>€ 579.73</td>
<td>€ 998.71</td>
</tr>
</tbody>
</table>

A change in HbA1c of 1% corresponds to 11 mmol/mol. Mean HbA1c at baseline was 57 mmol/mol (7.4%) for the liraglutide-treated patients and 59 mmol/mol (7.5%) for the patients treated with standard insulin therapy (p = 0.42). NA = not available (HbA1c levels were measured every 8 weeks).
26 weeks when liraglutide is discontinued after an 8-week trial period in patients not showing an early response. Early response, defined by either ≥ 3% weight loss or ≥ 60% decrease in insulin dose, had high positive and negative predictive values for treatment response after 26 weeks. The costs of this 8-week trial period are € 250 for one patient. The analysis in this study may help in cost-controlling clinical decision-making by selecting those patients who are most likely to benefit from addition of a GLP-1 receptor agonist to insulin therapy.

Reimbursement for treatment with GLP-1 receptor agonists is limited because it is considered expensive.7,14 On the other hand, GLP-1 receptor agonist treatment may also yield indirect cost-savings: less hypoglycaemia, a decreased need for glucose monitoring, and cost-savings associated with improved glycaemic control, weight loss, simplification of diabetes treatment and potentially less cardiovascular complications.3,15 The present analysis only calculated direct costs associated with a relatively short treatment period of adding liraglutide to insulin. Replication in an independent cohort is necessary to reinforce our results. A complete cost-benefit analysis is complex and contains many undetermined factors, including a possible increase in costs on the longer term due to additional life years gained.

Earlier studies have assessed the cost-effectiveness of GLP-1 receptor agonists in general and of liraglutide in particular, but mainly in comparison with other glucose-lowering therapies.8,16,17 The evidence review group from NICE reported an estimated cost-effectiveness of £ 15,130 per quality adjusted life year (QALY) for liraglutide 1.8 mg compared with insulin glargine.18 The investigators conducted additional sensitivity analyses and concluded that the factors that carried most weight in the comparison with glargine were the direct utility effects of body mass index changes and systolic blood pressure, underlining the significance of body weight. One other study assessed the cost-effectiveness of adding a GLP-1 receptor agonist to insulin and showed that the addition of lixisenatide to basal insulin treatment was associated with increased QALYs and reduced lifetime healthcare costs as compared with the addition of bolus insulin.19 These results support our previously reported findings of improved quality of life with liraglutide.7 Because liraglutide is more effective in weight loss and lowering HbA1c than lixisenatide,20,21 its potential benefits are greater. Nevertheless, outcomes of cost-efficiency calculations are largely dependent on assumptions regarding long-term benefits.22 While our treatment strategy yields less direct costs, our data can determine neither potential gain in QALYs nor their costs.

In this study, the cut-off points chosen can be regarded as arbitrary, but they were based on clinical reasoning. Thus, we chose the HbA1c cut-point as this is still the most widely recommended glycaemic target for patients with type 2 diabetes,1 and stopping of insulin because of its implications for daily management. A 4% weight loss was chosen because this was the average weight gain in patients starting on insulin treatment.2 In a recent study among patients with type 2 diabetes, a gain in body weight of ≥ 5% was associated with a 14% increase in medical costs, when glycaemic control was suboptimal (HbA1c ≥ 53 mmol/mol [7%]).23 Some may consider the clinical impact of 4% weight loss to be limited, but a minimal weight reduction of 3.5% in obese participants is already associated with a clinically relevant improvement in cardiometabolic health.24,25 Moreover, weight loss is considered to be very important by patients and is associated with higher treatment satisfaction, better treatment adherence and a healthier lifestyle.26-28

In the present analysis we have used quite strict criteria in defining treatment success. Current guidelines advise to aim for less strict treatment targets, especially concerning HbA1c in elderly people.1 The NICE guidelines define a beneficial response to GLP-1 receptor agonists as an HbA1c reduction of at least 11 mmol/mol (1%) or a weight loss of at least 3% after 26 weeks of treatment.8 Although one of the four ‘non-responders’ at 8 weeks in our trial stopped treatment because of adverse events, the three remaining subjects all had clinical responses at week 26 that many clinicians would view as clinically relevant. One 64-year old patient showed a 6.5% weight loss with a stable HbA1c of 58 mmol/mol (7.5%), another patient showed a 2.2% weight loss in combination with an 8.7 mmol/mol (0.8%) decrease in HbA1c and the third patient lost 3.9% of body weight and had an HbA1c decrease of 14 mmol/mol (1.3%). Surely, less strict targets could be applied, but such would result in more people being eligible for treatment, thereby increasing overall treatment costs.

Our findings extend those of a previous study on the predictive value of short-term weight loss with a GLP-1 receptor agonist to a more generic good response in the longer term and an earlier decision time point. Subgroup analyses of the SCALE diabetes trial, in which overweight or obese patients with diabetes were treated with liraglutide 3.0 mg, showed that an early (within 16 weeks) loss of > 5% of initial body weight with liraglutide was a good predictor of clinically meaningful weight loss after one year of treatment.20,29 In the present analysis, we show that the weight response after 8 weeks of such treatment may suffice and not only predicts a good weight but also a good

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glycaemic effect (either reduction of HbA1c or cessation of insulin therapy). This time point may aid the clinician in making treatment decisions with respect to continuation or discontinuation of GLP-1 receptor agonists. HbA1c did not discriminate between responders and non-responders, which might be explained by the relatively low HbA1c at baseline, the study protocol that was aimed at reducing body weight rather than HbA1c, and the fact that time is needed for HbA1c to respond. As current guidelines, such as the NICE guideline, mostly advocate a trial period for GLP-1 receptor agonists of 26 weeks, our approach would lead to a substantial decrease in costs.

The strength of the present analysis is that we were able to calculate additional treatment costs in a real-life situation, which might be helpful in clinical decision-making. Our strategy to select patients with prominent treatment responses that are likely to translate into long-term clinical benefit was associated with € 1100 per successfully treated patient for the first 6 months and € 1900 for each treatment year thereafter. The present analysis also has limitations. Our model includes several assumptions that may affect outcomes. For example, the current assumption of needing four test strips per week probably underestimated the actual use of strips, particularly in patients assigned to continuing standard insulin therapy on premixed or basal-bolus insulin regimens. None of these patients could simplify insulin treatment, which contrasts with three patients in the liraglutide group who simplified from basal-bolus to basal insulin alone. We also did not consider the drop in costs associated with the cessation of oral glucose-lowering agents in five patients on liraglutide versus none in the standard insulin group. Neither did we model the costs associated with adverse gastrointestinal events. Although these were mild to moderate and of relatively short duration, we cannot fully exclude loss of labour productivity and absence from work. These side effects should be balanced with the reduced risk of hypoglycaemia relative to better glycaemic control with GLP-1 receptor agonist treatment, which is also associated with substantial direct and indirect medical costs. Only one severe adverse event (myocardial infarction) occurred, which was deemed unrelated to the study drug. We were not able to identify lifelong costs, which may change as cardiovascular outcome improves, and as the effects of liraglutide on body weight and decrease in HbA1c tend to diminish over time. Finally, the analysis was based on selected patients who may not necessarily be representative for the entire diabetes population.

In conclusion, an 8-week trial period of adding liraglutide to insulin in patients with pronounced insulin-associated weight gain is a good strategy to control costs, when patients not showing ≥ 3% weight loss or ≥ 60% decrease in insulin dose discontinue such treatment. With prolonged treatment, costs are likely to decrease further due to a reduction in long-term diabetes complications mediated by weight loss and better glycaemic control.

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DISCLOSURES

The ELEGANT trial was an investigator-initiated trial that was funded in part by Novo Nordisk B.V. (Alphen aan den Rijn, the Netherlands). Novo Nordisk also provided the medication. Novo Nordisk had no role in the design of the ELEGANT trial, or the collection, management, analysis and interpretation of the data and also no role in the present analysis, the writing of this manuscript or the decision to submit the paper for publication.

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REFERENCES


The current total economic burden of diabetes mellitus in the Netherlands

M.L. Peters¹, E.L. Huisman²*, M. Schoonen², B.H.R. Wolffenbuttel³

¹Real World Strategy & Analytics, Mapi Group, Houten, the Netherlands, ²Novo Nordisk, Alphen aan den Rijn, the Netherlands, ³Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, *ehui@novonordisk.com

ABSTRACT

Introduction and aim: Insight into the total economic burden of diabetes mellitus (DM) is essential for decision makers and payers. Currently available estimates for the Netherlands only include part of the total burden or are no longer up-to-date. Therefore, this study aimed to determine the current total economic burden of DM and its complications in the Netherlands, by including all the relevant cost components.

Methods: The study combined a systematic literature review to identify all relevant published information and a targeted review to identify relevant information in the grey literature. The identified evidence was then combined to estimate the current total economic burden.

Results: In 2016, there were an estimated 1.1 million DM patients in the Netherlands, of whom approximately 10% had type 1 and 90% had type 2 DM. The estimated current total economic burden of DM was €6.8 billion in 2016. Healthcare costs (excluding costs of complications) were €1.6 billion, direct costs of complications were €1.3 billion and indirect costs due to productivity losses, welfare payments and complications were €4.0 billion.

Conclusion: DM and its complications pose a substantial economic burden to the Netherlands, which is expected to rise due to changing demographics and lifestyle. Indirect costs, such as welfare payments, accounted for a large portion of the current total economic burden of DM, while these cost components are often not included in cost estimations. Publicly available data for key cost drivers such as complications were scarce.

KEYWORDS

Cost of illness, diabetes mellitus, economic burden, the Netherlands

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases in the Netherlands.¹ It has two primary forms, type 1 and type 2. Type 1 DM (T1DM) is an autoimmune disorder, affecting approximately 10% of those with DM, in which the body's ability to produce insulin is severely disturbed. It is usually diagnosed in children or young adults, but it can become manifest at any age, with the exact cause of the disease still unknown.¹ Type 2 DM (T2DM) is the most common form of DM, affecting approximately 90% of those with DM. The causes of T2DM are multifactorial and include both impaired insulin secretion, and a resistance of the body to the effect of insulin, resulting in hyperglycaemia.² It usually occurs in adults over 40, but is increasingly seen at younger ages. Risk factors for T2DM include obesity, physical inactivity, poor nutrition, genetic predisposition, and a family history of DM.¹,²,³ DM is associated with a number of disabling long-term complications due to consistently elevated blood glucose levels, such as cardiovascular disease, retinopathy, neuropathy, kidney failure and lower-limb amputation. These complications have a significant impact on patients’ quality of life.⁴⁻⁶ Furthermore, anti-hyperglycaemic agents, particularly insulin, can additionally lead to minor or major hypoglycaemia.⁷ Treatment of T2DM in particular is challenging, as it is multidimensional, often involves multiple caregivers and includes immediate lifestyle changes and treatment in order to prevent or delay the occurrence of complications many years later.⁸ Optimal self-management and adherence to DM medication remains an ongoing issue.⁹ DM is a growing problem for society. In 2014 there were an estimated 1,078,400 diagnosed DM patients in the Netherlands.¹ From 2000 to 2007, the DM prevalence rose by 55%, from 480,000 patients in 2000 to 740,000 in 2007, due to a combination of demographics, lifestyle factors and enhanced detection methods. A projection
published in 2009 estimated that the DM prevalence would increase to 1,320,000 patients in 2025.22 DM is associated with a substantial economic burden.3,11,14 The total economic burden of DM includes the direct costs of treating the illness, but it also includes the costs of treating DM complications, the costs of productivity losses due to DM and its complications, and the costs of welfare payments due to DM-related disability. Insight into the current total economic burden of DM and its complications is essential for decision makers and payers, especially in this era of rising health expenditures, pressure on payers and initiatives for cost reduction. Understanding the total economic burden of a disease and the cost components that make up this burden is crucial in order to make informed policy decisions. Furthermore, a complete overview of the economic burden of DM may help physicians making informed decisions regarding disease-specific care.15

Unfortunately, the currently available estimates of the total economic burden of DM and its complications in the Netherlands only include parts of the total burden or are no longer up-to-date.14,49 For instance, an estimate of the healthcare costs due to DM was published by the Dutch National Institute of Public Health and the Environment (RIVM) in 2011 and did not include the cost of complications, productivity loss costs or welfare payment costs.1 A study by Booz & Company did include all cost components making up the total economic burden of DM, but was published in 2010.46 Other cost estimates are more recent, but only focus on the costs of DM medication and/or monitoring.15-18,19 Therefore, the aim of this study was to determine the current total economic burden of diabetes mellitus and its complications in the Netherlands, by including all relevant cost components, such as healthcare costs, costs of complications and indirect costs.

MATERIALS AND METHODS

Systematic literature review and targeted review
This study combined a systematic literature review (SLR) and a targeted review to maximise the likelihood that all available evidence relating to the current total economic burden of DM and its complications in the Netherlands was identified. To identify all relevant published information, a SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.23 MEDLINE, EMBASE, ECONLIT, NHS EED and HTA databases were searched on 8 September 2015 (table A.1 in Appendix A). The search was restricted to records published from January 2010 onwards to ensure that the most recent data were included. Study selection took place based on pre-defined criteria regarding the population, outcomes and study design of interest (table A.2 in Appendix A). The population of interest consisted of T1DM or T2DM patients, and/or patients with microvascular or macrovascular DM complications of any grade. All studies reporting costs, resource use and work productivity in relation to the Netherlands were of interest. The SLR identified 572 records, of which 42 publications were retrieved for full-text screening and 12 studies were included for data extraction.43-45 Figure A.3 in Appendix A shows the PRISMA flow diagram of the study selection process.24

In addition to the SLR, a targeted review was set up to search for relevant information in the grey literature. This search was performed during October and November 2015, and updated in May 2016. Three different types of information were of interest and for each type, different pre-selected sources were searched: 1) DM treatment guidelines;33-40 2) incidence and prevalence estimates of T1DM, T2DM and DM complications in the Netherlands;4,14,41-43 3) costs and resource use associated with DM and its complications in the Netherlands.14,43-45,49-49 Of these pre-selected sources, eight provided data that were used in the estimation of the current total economic burden.2,15,44-45,48,49 In addition, targeted searches were undertaken to fill any data gaps for which no information was identified in the SLR or the targeted review of pre-selected sources. Seven sources were used to fill data gaps.30-56

The evidence identified in the SLR and targeted review was then combined to estimate the current total economic burden of DM and its complications in the Netherlands. A detailed overview of the data used in the estimation is provided in tables B.1 to B.6 in Appendix B.

Estimation of DM incidence and prevalence
The number of DM patients in the Netherlands in 2016 was estimated based on the Dutch population size in 2016 and the DM prevalence rate in representative general practitioner (GP) practices.14,41 The estimate of the annual DM incidence was also based on these sources.44-45 The proportion of patients with T1DM and T2DM among the total number of DM patients was based on a website coordinated by the RIVM.15 The annual mortality rate for DM patients was estimated by combining the rate of DM-specific mortality and the mortality rate for the Dutch general population.14,41-43

Estimation of direct healthcare costs
The estimation of direct healthcare costs included DM specific costs for medication, monitoring and treatment devices (including consumables), primary care, hospital care, mental care and elderly care.
Medication costs were estimated based on the number of users per treatment, the number of daily defined doses (DDD) per user per year and the cost per DDD. Medication costs were only applied to the proportion of DM patients treated with medication, given that T2DM patients are initially treated with lifestyle and dietary advice. Therefore, the patients not treated with medication were considered to consist solely of T2DM patients, as T1DM patients would always be receiving insulin. The proportion of DM patients treated with medication was estimated based on the difference between the total number of DM medication users and the total number of DM patients. Because data were only available for DM in total, the number of insulin users for T1DM and T2DM separately was derived by applying a proportion based on FiScript data. Costs for other DM medications besides insulin were only applied to the population of T2DM patients.

The costs of monitoring, diagnostic and treatment devices (including consumables) were estimated based on the number of device users, the average number of prescriptions per user and the cost per prescription. These costs were only applied to the proportion of DM patients treated with medication, as these patients require stringent monitoring of their disease and they also use treatment devices (e.g. insulin pumps, syringes, injection pens), while patients solely treated with lifestyle and dietary advice do not. As data were only available for DM in total, the costs for T1DM and T2DM separately were derived by applying proportions based on FiScript data.

Primary care costs included the costs of DM-related visits to GPs, DM nurses, dieticians, podiatrists and physical therapists. The costs of GP visits were estimated based on DM-specific resource use from representative GP practices and Dutch reference prices. For GP consultations occurring out-of-office hours, an average of the tariffs from all Dutch provinces was applied. DM nurse, dietician, podiatrist and physical therapist resource use was based on a study in T2DM patients by Van der Heijden et al. It was assumed based, on expert opinion (due to the lack of published data), that these were representative for the total DM population. Unit costs were based on Dutch reference prices or retrieved from this same study. Hospital care costs included the costs of DM-related medical specialist outpatient visits and hospitalisations. The costs of outpatient visits were estimated based on DM-specific resource use and Dutch reference prices. Resource use for visits to all medical specialists except internal medicine was based on Van der Heijden et al. Different resource use rates were applied for internal medicine outpatient visits, because of expected differences in treatment patterns between T1DM and T2DM. These were based on expert opinion (due to the lack of published data) for T1DM and data from Van der Heijden et al. for T2DM. The costs of DM-related hospitalisations and day admissions were estimated based on DM-specific resource use and Dutch references prices. Resource use for day admissions and hospitalisations was based on data published by Statistics Netherlands.

Mental care costs were estimated based on resource use in T2DM patients, the average number of visits in representative mental care practices and the Dutch reference price. It was assumed, based on expert opinion (due to the lack of published data), that this resource use was representative for the total DM population.

Elderly care costs were included separately in the cost estimation, because the DM prevalence in nursing homes is two to three times higher than the prevalence in GP practices and approximately 15% of patients in nursing homes have DM, with more frequent macrovascular complications than in the overall DM patient population. Elderly care costs were included as a cost per patient per year, estimated based on the total DM elderly care costs for 2011 published by the RIVM and the total number of DM patients in 2011.

**Estimation of costs of complications**

The direct costs of complications were estimated based on annual complication rates and the direct costs of the respective complications. The rates of long-term DM complications were based on an international DM registry, as no Dutch data were publicly available. As the registry only provided data for T2DM it was assumed, based on expert opinion (due to the lack of published data), that these were representative of the total DM population. The rate of major hypoglycaemia was based on Dutch data. All T1DM patients were assumed to use insulin and therefore at risk of major hypoglycaemia. For T2DM, the number of patients at risk (e.g. insulin users) was based on Pharmo and FiScript data. Direct costs of complications were based on a study by Van Haalen et al. in T2DM, which in turn retrieved cost data from several publications. The direct costs of a T2DM complication were assumed to be representative for the total DM population.

**Estimation of indirect costs**

The estimation of indirect costs included productivity loss costs, welfare payment costs and indirect costs of complications. Productivity loss costs from paid work and due to premature mortality were included, and both were based on the percentage of working age patients, the employment rate, eight working hours per day and the reference cost for productivity per hour. Productivity loss costs from paid work were further based on the annual percentage of patients taking sick days and the average number of sick days taken. Productivity loss costs due to premature mortality were estimated using the friction
cost method and further based on the rate of DM specific mortality, the full-time equivalent rate and a friction period of 85 days.\(^{2,3,4,5,6}\)

Welfare payment costs were estimated based on the percentage of working age patients, the percentage of patients with disability, the proportion of patients with complete or partial disability, an assumed 50% disability level for patients with partial disability, the Dutch modal income and a welfare payment level of 70% of the last salary.\(^{4,43,44,45,46}\)

For the estimation of the indirect costs of DM complications, the same complication rates were used as for the direct costs.\(^{7,8,9,10,11,12,13}\) The direct costs of complications included the medical costs associated with the complications of DM and travel expenses; the indirect costs of complications included the productivity losses associated with the DM complications based on the friction cost method.\(^{7,8,9,10}\) These indirect costs were included separately because absenteeism due to DM complications is often not linked back to DM itself. Indirect costs of complications were based on a study by Van Haalen et al., that in turn retrieved cost data from several publications.\(^{7,8,9,10,11,12,13,14,15}\) The indirect costs of a T2DM complication were assumed representative for the total DM population.

In the cases where data were only available for DM in total, the costs for T1DM and T2DM separately were derived by applying their respective proportion (T1DM: 10% of total; T2DM: 90% of total) to the total cost estimate for DM.\(^{16}\) All costs were inflated to 2016 euros based on the consumer price index published by Statistics Netherlands.\(^{47}\)

**RESULTS**

**DM incidence and prevalence**

There were an estimated 1,098,609 patients with DM in the Netherlands in 2016 (table 1), based on a DM prevalence rate of 6.47% in representative GP practices in 2014 and on the population size of the Netherlands on 1 January 2016 (16,980,049 inhabitants).\(^{48,49}\) Of these patients, 10% (109,861 patients) were estimated to have T1DM and 90% (988,748 patients) to have T2DM.\(^{50}\) In accordance with the guidelines for T2DM, a substantial proportion of T2DM patients were considered to be initially treated with lifestyle and dietary advice and therefore not yet treated with medication,\(^{8}\) whereas all T1DM patients start insulin treatment immediately after diagnosis (table 1). The DM incidence rate was reported to be 0.36% in representative GP practices in 2014, amounting to 61,128 new DM patients in 2016, based on the size of the Dutch population in 2016.\(^{48,49}\)

| Table 1. Estimated prevalence of diabetes mellitus in the Netherlands |
|--------------------------|--------------------------|--------------------------|
| Category | 2016 |
| DM | T1DM | T2DM |
| Prevalence rate | 6.47% | 0.65% | 5.82% |
| Total number of patients | 1,098,609 | 109,861 | 988,748 |
| Number of patients treated with medication | 806,524 | 109,861 | 696,663 |

DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

**DM costs**

The current total economic burden of DM in the Netherlands was estimated to be € 6.8 billion in 2016. For T1DM and T2DM separately, the current total economic burden was estimated to be € 873 million and € 5.9 billion, respectively (table 2).

**Estimation of direct healthcare costs**

The healthcare costs (excluding costs of complications) made up 23.1% (€ 1.6 billion) of the total costs for DM. The main cost drivers were elderly care costs (€ 496 million), primary care costs (€ 311 million) and hospital care costs (€ 277 million). For T1DM, the healthcare costs (excluding costs of complications) amounted to 35.5% (€ 310 million) of the total costs. The main cost drivers were monitoring/device costs (€ 121 million), medication costs (€ 57 million), hospital care costs (€ 50 million) and elderly care costs (€ 50 million). For T2DM, the healthcare costs (excluding costs of complications) were 21.3% (€ 1.3 billion) of the total costs. The main cost drivers were elderly care costs (€ 447 million), primary care costs (€ 280 million) and hospital care costs (€ 227 million).

**Estimation of costs of complications**

The direct costs of complications made up 18.7% (€ 1.3 billion) of the total costs for DM. The most costly complications were end-stage renal disease (€ 563 million), stroke (€ 323 million) and myocardial infarction (€ 128 million). For T1DM, the direct costs of complications made up 20.8% (€ 162 million) of the total costs. The most costly complications were end-stage renal disease (€ 56 million), major hypoglycaemia (€ 40 million) and stroke (€ 32 million). For T2DM, the direct costs of complications amounted to 18.5% (€ 1.1 billion) of the total costs. The most costly complications were end-stage renal disease (€ 506 million), stroke (€ 290 million) and myocardial infarction (€ 115 million).

**Estimation of indirect costs**

For DM in total, the productivity loss costs amounted to 9.5% (€ 648 million) of the total costs, the welfare payment...
Peters et al. The Dutch economic burden of diabetes mellitus.

**DISCUSSION**

This study aimed to determine the current total economic burden of DM and its complications in the Netherlands to inform decision makers and payers. The total economic burden in 2016 was found to be substantial, with an estimated total cost of €6.8 billion. More than half of this total cost (€4.0 billion) was attributable to indirect costs (productivity losses, welfare payments and complications), with welfare payments being the largest contributor to the indirect costs (€3.0 billion). Therefore, measures or strategies aimed at reducing these indirect costs could result in substantial cost-savings. Furthermore, the healthcare costs due to DM and its complications were €2.8 billion (41.8% of the total cost), which constitutes approximately 3.0% of the total health expenditure in the Netherlands (€95.3 billion in 2015, no data available for 2016). Moreover, it is likely that the total economic burden of DM and its complications will rise further due to changes in demographics and lifestyle.

The results of our study can be compared with those of previous studies. A study by Booz & Company on diabetes care in the Netherlands reported substantially higher medical and total costs (€4.5 and 10-11 billion in 2010 euros, respectively) than estimated in our study. It should be noted that the Booz & Company study has not been published in a nationally or internationally published peer-reviewed paper and that their results should therefore
The main strength of this study is the inclusion of all cost components that make up the current total economic burden of DM in the Netherlands, such as healthcare costs, costs of complications and indirect costs. Furthermore, the combination of a systematic literature review and a targeted review maximised the likelihood that all available evidence was identified. However, certain limitations of this study have to be noted. Firstly, the evidence identified was fragmented, requiring the use of several assumptions, the use of aggregated data and the combination of data from several sources. Secondly, because no single source could provide all the data required to estimate the current total economic burden, data from several sources had to be combined. Although care was taken to avoid double counting, the use of (aggregated) data from several sources inherently includes the risk that certain cost items may have been double counted. Thirdly, data for T1DM and T2DM separately were scarce, most sources only reported data for DM in total. Therefore, the estimation of the current total economic burden for T1DM and T2DM separately was predominantly based on the respective prevalence amongst the total number of DM patients (T1DM: 10% of total; T2DM: 90% of total). Despite this limitation, the separate results for T1DM and T2DM, although more uncertain than the results for DM in total, still provide valuable insight into the contribution of T2DM to the total economic burden for DM, which can inform health policy decisions, as T2DM is for a large part a preventable disease. Fourthly, this study only included costs for DM medications, while 85% of T2DM patients suffer from at least one other chronic condition at the time of diagnosis and 30% of DM patients have comorbid cardiovascular disease and 17.7% have comorbid chronic obstructive pulmonary disease. Therefore, the estimated €2.8 billion in healthcare costs is most likely still an underestimation of the total healthcare costs accrued by DM patients. Finally, there were no Dutch publicly available data regarding the rates of long-term DM complications, requiring the use of data from an international DM registry.

The results of this study highlight the increasing costs of DM associated with increasing DM prevalence. Initiatives aimed at preventing T2DM have been largely unsuccessful; however, such initiatives, if successful, would help to stem the rising costs. Furthermore, this study shows that the indirect costs related to productivity losses, welfare payments and complications account for more than half of DM’s current total economic burden. These indirect costs are mainly related to the long-term complications of DM and the disability that these cause. In addition to the substantial costs associated with these complications, they are also shown to have a significant impact on patients’ quality of life. These findings indicate that there is great potential for gain, both in terms of cost savings and improvements in patients’ quality of life, by reducing the occurrence of the long-term complications of DM. For example, improvements in the management of DM and adherence to medication from early in the course of the disease will lead to better long-term glycaemic control and DM-related complications.
CONCLUSION

Diabetes mellitus and its complications pose a substantial economic burden to the Netherlands, with the burden expected to rise further due to changing demographics and lifestyle. Indirect costs, such as welfare payments, accounted for a large portion of the current total economic burden of diabetes mellitus, while these cost components are often not included in cost estimations. Publicly available data for key cost drivers such as long-term complications were scarce.

DISCLOSURES

Mapi Group was financially supported by Novo Nordisk to perform the study. M.L. Peters is a Mapi employee and served as a paid consultant to Novo Nordisk during the conduct of this study; E.L. Huisman and M. Schoonen are Novo Nordisk employees; B.H.R. Wolfenbuttel has received grant support for clinical studies and also consulting fees for serving on advisory boards and as a speaker for Amgen, Astra Zeneca, Eli Lilly and Company, Novo Nordisk, Pfizer and Sanofi. He has also received consulting fees from Eli Lilly and Company as a member of the 4B study and of the DURABLE Trial Data Monitoring Committee.

REFERENCES


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Netherlands Journal of Medicine
APPENDIX A: SYSTEMATIC LITERATURE REVIEW

<table>
<thead>
<tr>
<th>#</th>
<th>Search terms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp Diabetes Mellitus/</td>
<td>930439</td>
</tr>
<tr>
<td>2</td>
<td>diabet$.tw.</td>
<td>1028696</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>1212523</td>
</tr>
<tr>
<td>4</td>
<td>cost of illness/</td>
<td>36201</td>
</tr>
<tr>
<td>5</td>
<td>(cost? or costing?) or costly or costed),tw.</td>
<td>9777572</td>
</tr>
<tr>
<td>6</td>
<td>(price? or pricing?),tw.</td>
<td>205828</td>
</tr>
<tr>
<td>7</td>
<td>(pharmacoeconomic? or (pharmaco adj economic?)),tw.</td>
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<td>8</td>
<td>budget$.tw.</td>
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<td>9</td>
<td>expenditure$.tw.</td>
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<td>10</td>
<td>(value adj (money or monetary)),tw.</td>
<td>1341</td>
</tr>
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<td>11</td>
<td>(fee or fees),tw.</td>
<td>34294</td>
</tr>
<tr>
<td>12</td>
<td>(&quot;resource use&quot; or &quot;resource consumption&quot;),tw,ab.</td>
<td>22224</td>
</tr>
<tr>
<td>13</td>
<td>(&quot;use&quot; or &quot;health&quot; or &quot;health$&quot; or &quot;resource$&quot;) adj3 &quot;measurement&quot;),tw,ab.</td>
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</tr>
<tr>
<td>14</td>
<td>(&quot;health$&quot; adj3 &quot;use&quot;),tw,ab.</td>
<td>55991</td>
</tr>
<tr>
<td>15</td>
<td>(&quot;hospital&quot; or &quot;doctor&quot; or “GP” or “general practitioner” or “nurse” or “clinic” or &quot;surgery&quot;) adj3 (&quot;use&quot; or &quot;visit$&quot; or &quot;attendance&quot; or &quot;admission&quot; or &quot;readmission&quot;),tw,ab.</td>
<td>113853</td>
</tr>
<tr>
<td>16</td>
<td>(productiv$ adj3 loss),tw.</td>
<td>403</td>
</tr>
<tr>
<td>17</td>
<td>or/4-16</td>
<td>1442770</td>
</tr>
<tr>
<td>18</td>
<td>exp netherlands/ or europe/</td>
<td>293024</td>
</tr>
<tr>
<td>19</td>
<td>(dutch or netherland$ or holland or europe),tw.</td>
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<td>20</td>
<td>18 or 19</td>
<td>489391</td>
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<td>21</td>
<td>3 and 17 and 20</td>
<td>1489</td>
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<td>limit 21 to yr=&quot;2010 -Current&quot;</td>
<td>739</td>
</tr>
<tr>
<td>23</td>
<td>remove duplicates from 22</td>
<td>572*</td>
</tr>
</tbody>
</table>

*4-16 is a search filter for economic studies appraised by the InterTASC Information Specialists’ Sub-Group. The search terms were combined using ‘OR’ in #1 (‘1 or 2’), #17 (‘or/4-16’) and #20 (‘18 or 19’). These three components of the search strategy were then combined using ‘AND’ in #21 (‘3 and 17 and 20’). The search retrieved 477 records from EMBASE, 76 from MEDLINE, 17 from NHS EED, 2 from ECONLIT and 0 from HTA. Please note that these are the number of records retrieved after duplicates were removed using the Ovid® platform (#23: remove duplicates from 22), which removed 167 duplicates.

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### Table A.2. Criteria for selection of studies in the systematic literature review

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPULATION</td>
<td>Patients with type 1 or type 2 DM</td>
<td>Healthy patients / controls</td>
</tr>
<tr>
<td></td>
<td>Children or adults</td>
<td>Patients without type 1 or type 2 DM</td>
</tr>
<tr>
<td></td>
<td>Patients with micro- or macro-vascular DM complications of any grade</td>
<td></td>
</tr>
<tr>
<td>INTERVENTIONS</td>
<td>No selection was made on interventions</td>
<td>No selection was made on interventions</td>
</tr>
<tr>
<td>COMPARATOR</td>
<td>No selection was made on comparator</td>
<td>No selection was made on comparator</td>
</tr>
<tr>
<td>OUTCOMES</td>
<td>Costs</td>
<td>Outcomes from outside Europe HRQoL / utilities</td>
</tr>
<tr>
<td></td>
<td>Resource use (medical, non-medical)</td>
<td>All other outcomes not listed under ‘inclusion’</td>
</tr>
<tr>
<td></td>
<td>Work productivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Studies with incidence and prevalence data were flagged</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Costs</td>
<td>Outcomes from outside the Netherlands HRQoL / utilities</td>
</tr>
<tr>
<td></td>
<td>Resource use (medical, non-medical)</td>
<td>All other outcomes not listed under ‘inclusion’</td>
</tr>
<tr>
<td></td>
<td>Work productivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Studies with incidence and prevalence data were flagged</td>
<td></td>
</tr>
<tr>
<td>STUDY DESIGN</td>
<td>Economic studies (e.g. cost of illness, burden of disease, budget impact,</td>
<td>Animal studies</td>
</tr>
<tr>
<td></td>
<td>cost-effectiveness and cost-utility analyses)</td>
<td>In vivo and in vitro studies</td>
</tr>
<tr>
<td></td>
<td>Cost analyses</td>
<td>Biomarker and genetic studies</td>
</tr>
<tr>
<td></td>
<td>Health technology assessments that include economic data</td>
<td>Guidelines</td>
</tr>
<tr>
<td></td>
<td>Studies reporting economic data</td>
<td>Reviews, letters, (case) report, expert opinion, discussion papers, editorials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conference abstracts from &lt;2013*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SLR and NMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase I clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methodology studies or protocols</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus; HRQoL = health-related quality of life; NMA = network meta-analysis; SLR = systematic literature review. *Conference abstracts published before 2013 were excluded, as it was assumed that studies presented as an abstract before 2013 would have become available as a full-text publication within this time-frame.
Figure A.3. Flow diagram of the study selection process in the systematic literature review

Search strategy (Ovid®):
MEDLINE & MEDLINE In-Process: 76 abstracts retrieved
EMBASE: 477 abstracts retrieved
ECONLIT: 2 abstracts retrieved
NHS EED: 17 abstracts retrieved
HTA: 0 abstracts retrieved

572 abstracts retrieved for abstract screening

Abstracts excluded: 530
Patient pop. not of interest (173)
Intervention not of interest (0)
Comparator not of interest (0)
Outcomes not of interest (105)
Study design not of interest (120)
Conference <2013 (81)
Duplicate (51)

42 publications selected for full text screening
39 full text articles
3 conference abstracts

Articles excluded: 30
Patient pop. out of scope (3)
Intervention out of scope (0)
Comparator out of scope (0)
Outcomes out of scope (23)
Study design out of scope (4)
Superseded (0)

12 publications retrieved for data extraction
APPENDIX B. DATA USED FOR THE ESTIMATION OF THE CURRENT TOTAL ECONOMIC BURDEN OF DIABETES MELLITUS AND ITS COMPLICATIONS IN THE NETHERLANDS

Table B.1. Epidemiological data

<table>
<thead>
<tr>
<th>Category</th>
<th>Data input</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Dutch population on 1 January 2016</td>
<td>16,980,049</td>
<td>[2]</td>
</tr>
<tr>
<td>Prevalence of DM</td>
<td>6.5%</td>
<td>[3]</td>
</tr>
<tr>
<td>Prevalence of type 1 DM amongst total DM population</td>
<td>10.0%</td>
<td>[4, 5]</td>
</tr>
<tr>
<td>Prevalence of type 2 DM amongst total DM population</td>
<td>90.0%</td>
<td>[4, 5]</td>
</tr>
<tr>
<td>Incidence of DM</td>
<td>0.4%</td>
<td>[3]</td>
</tr>
<tr>
<td>Incidence of type 1 DM amongst total DM population</td>
<td>10.0%</td>
<td>Assumed identical to the prevalence distribution</td>
</tr>
<tr>
<td>Incidence of type 2 DM amongst total DM population</td>
<td>90.0%</td>
<td>Assumed identical to the prevalence distribution</td>
</tr>
<tr>
<td>Proportion of DM patients not treated with medication (assumed to consist solely of type 2 DM patients)*</td>
<td>26.6%</td>
<td>Calculation based on [2, 3, 6]</td>
</tr>
<tr>
<td>Annual curative disease rate</td>
<td>0.0%</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Annual mortality rate**</td>
<td>1.1%</td>
<td>Calculation based on [2-4]</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus.

*The proportion of DM patients not treated with medication was calculated by dividing the number of patients not treated with medication by the total number of DM patients in 2014. The number of patients not treated with medication was calculated by subtracting the number of DM medication users from the total number of DM patients in 2014 (2014 data).

**The annual mortality rate was calculated by combining the DM specific mortality rate with the mortality rate the Dutch general population. The DM specific mortality rate was calculated by dividing the total number of deaths due to DM in 2014 by the total number of DM patients in 2014.

Table B.2. Medication data

<table>
<thead>
<tr>
<th>Medicaments &amp; ATC-codes</th>
<th>Market share*</th>
<th># of patients receiving respective treatment in 2016**</th>
<th>Cost per user per year*** (2016 €)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>A10AB01 fast acting insulin (human)</td>
<td>0.4%</td>
<td>2989 959 2030</td>
<td>€ 316.36</td>
<td>[6,7]</td>
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<tr>
<td>A10AB04 fast acting insulin lispro</td>
<td>2.0%</td>
<td>15,866 5089 10,777</td>
<td>€ 476.52</td>
<td>[6,7]</td>
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<tr>
<td>A10AB05 fast acting insulin aspart</td>
<td>16.6%</td>
<td>133,698 42,884 90,814</td>
<td>€ 380.65</td>
<td>[6,7]</td>
</tr>
<tr>
<td>A10AB06 insulin glulisine</td>
<td>1.5%</td>
<td>11,873 3808 8065</td>
<td>€ 349.82</td>
<td>[6,7]</td>
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<tr>
<td>A10AC01 intermediate acting insulin (human)</td>
<td>0.3%</td>
<td>2801 898 1902</td>
<td>€ 207.59</td>
<td>[6,7]</td>
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<tr>
<td>A10AD01 premixed insulin (human)</td>
<td>0.3%</td>
<td>2135 685 1450</td>
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<tr>
<td>A10AD04 premixed insulin lispro</td>
<td>0.3%</td>
<td>2067 663 1404</td>
<td>€ 528.12</td>
<td>[6,7]</td>
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<tr>
<td>A10AD05 premixed insulin aspart</td>
<td>7.1%</td>
<td>57,589 18,472 39,117</td>
<td>€ 530.81</td>
<td>[6,7]</td>
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<tr>
<td>A10AE04 insulin glargine</td>
<td>15.1%</td>
<td>121,613 39,008 82,605</td>
<td>€ 455.17</td>
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<td>A10AE05 insulin detemir</td>
<td>6.2%</td>
<td>50,207 16,104 34,103</td>
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<td>A10AE06 insulin degludec</td>
<td>0.0%</td>
<td>234 75 159</td>
<td>€ 142.33</td>
<td>[6,7]</td>
</tr>
<tr>
<td>A10BA02 metformin</td>
<td>78.2%</td>
<td>610,717 0 610,717</td>
<td>€ 38.25</td>
<td>Assumption, [6]</td>
</tr>
<tr>
<td>A10BB01 glibenclamide</td>
<td>0.7%</td>
<td>5262 0 5262</td>
<td>€ 61.07</td>
<td>Assumption, [6]</td>
</tr>
</tbody>
</table>

Peters et al. The Dutch economic burden of diabetes mellitus.
<table>
<thead>
<tr>
<th>Medicaments &amp; ATC-codes</th>
<th>Market share*</th>
<th># of patients receiving respective treatment in 2016**</th>
<th>Cost per user per year*** (2016 €)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM</td>
<td>Type 1 DM</td>
<td>Type 2 DM</td>
<td></td>
</tr>
<tr>
<td>A10BB03 tolbutamide</td>
<td>1.0%</td>
<td>7,701</td>
<td>7,701</td>
<td>€ 70.56</td>
</tr>
<tr>
<td>A10BB09 gliclazide</td>
<td>14.4%</td>
<td>116,394</td>
<td>116,394</td>
<td>€ 60.10</td>
</tr>
<tr>
<td>A10BB12 glimepiride</td>
<td>1.3%</td>
<td>10,273</td>
<td>10,273</td>
<td>€ 57.89</td>
</tr>
<tr>
<td>A10BD02 metformin and sulfonylureas</td>
<td>0.1%</td>
<td>484</td>
<td>484</td>
<td>€ 98.52</td>
</tr>
<tr>
<td>A10BD03 metformin and rosiglitazone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A10BD04 glimepiride and rosiglitazone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A10BD05 metformin and pioglitazone</td>
<td>0.0%</td>
<td>253</td>
<td>253</td>
<td>€ 410.70</td>
</tr>
<tr>
<td>A10BD07 metformin and sitagliptin</td>
<td>0.8%</td>
<td>6068</td>
<td>6068</td>
<td>€ 423.76</td>
</tr>
<tr>
<td>A10BD08 metformin and vildagliptin</td>
<td>0.6%</td>
<td>4990</td>
<td>4990</td>
<td>€ 434.77</td>
</tr>
<tr>
<td>A10BD10 metformin and saxaglipitin</td>
<td>0.0%</td>
<td>55</td>
<td>55</td>
<td>€ 346.86</td>
</tr>
<tr>
<td>A10BD11 metformin and linaglipitin</td>
<td>0.0%</td>
<td>141</td>
<td>141</td>
<td>€ 326.14</td>
</tr>
<tr>
<td>A10BD15 metformin and dapagliflozin</td>
<td>0.0%</td>
<td>42</td>
<td>42</td>
<td>€ 208.95</td>
</tr>
<tr>
<td>A10BF01 acarbose</td>
<td>0.2%</td>
<td>1481</td>
<td>1481</td>
<td>€ 120.79</td>
</tr>
<tr>
<td>A10BG02 rosiglitazone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A10BG03 pioglitazone</td>
<td>1.1%</td>
<td>8864</td>
<td>8864</td>
<td>€ 101.12</td>
</tr>
<tr>
<td>A10BH01 sitagliptin</td>
<td>2.8%</td>
<td>22,309</td>
<td>22,309</td>
<td>€ 445.81</td>
</tr>
<tr>
<td>A10BH02 vildagliptin</td>
<td>0.9%</td>
<td>7179</td>
<td>7179</td>
<td>€ 359.51</td>
</tr>
<tr>
<td>A10BH03 saxagliptin</td>
<td>0.3%</td>
<td>2,182</td>
<td>2,182</td>
<td>€ 453.75</td>
</tr>
<tr>
<td>A10BH05 linaglipitin</td>
<td>0.6%</td>
<td>5144</td>
<td>5144</td>
<td>€ 400.19</td>
</tr>
<tr>
<td>A10BX02 repaglinide</td>
<td>0.1%</td>
<td>654</td>
<td>654</td>
<td>€ 110.98</td>
</tr>
<tr>
<td>A10BX04 exenatide</td>
<td>0.2%</td>
<td>1533</td>
<td>1,533</td>
<td>€ 1,063.99</td>
</tr>
<tr>
<td>A10BX07 liraglutide</td>
<td>1.4%</td>
<td>10,915</td>
<td>10,915</td>
<td>€ 1,373.74</td>
</tr>
<tr>
<td>A10BX09 dapagliflozin</td>
<td>0.3%</td>
<td>1839</td>
<td>1839</td>
<td>€ 304.44</td>
</tr>
<tr>
<td>A10BX10 lixisenatide</td>
<td>0.0%</td>
<td>31</td>
<td>31</td>
<td>€ 246.66</td>
</tr>
<tr>
<td>A10BX11 canagliflozin</td>
<td>0.0%</td>
<td>96</td>
<td>96</td>
<td>€ 178.99</td>
</tr>
<tr>
<td>A10BX12 empagliflozin</td>
<td>0.0%</td>
<td>1</td>
<td>1</td>
<td>€ 32.46</td>
</tr>
</tbody>
</table>

ATC-code = Anatomical Therapeutic Chemical – code; DM = diabetes mellitus.
Costs were inflated to 2016 euros using inflation rates published by Statistics Netherlands.*
*Medication market shares were calculated by dividing the number of users per medicament by the total number of diabetes mellitus medication users (2014 data).**
**The number of type 1 and 2 DM patients receiving insulin was calculated by applying a proportion of insulin users for type 1 and 2 DM respectively (based on Pharmo/Farminform FiScript data) to the respective market shares. For all DM medications besides insulin, it was assumed that all users were type 2 DM patients.***
***The cost per user per year was calculated by multiplying the number of daily defined doses (DDD) per user per year with the cost per DDD (2014 data).
### Table B.3. Healthcare cost data

<table>
<thead>
<tr>
<th>Resource</th>
<th>% Use</th>
<th>Frequency</th>
<th>Unit cost</th>
<th>Cost per patient year (2016 €)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP contact for DM</td>
<td>5.4</td>
<td>1.4</td>
<td>€ 33.00</td>
<td>2014 € 47.43 3.8</td>
<td></td>
</tr>
<tr>
<td>Consult</td>
<td>26.4%</td>
<td>0.2</td>
<td>€ 50.00</td>
<td>2014 € 7.62                3.8</td>
<td></td>
</tr>
<tr>
<td>Home visit</td>
<td>2.8%</td>
<td>0.5</td>
<td>€ 17.00</td>
<td>2014 € 8.42                3.8</td>
<td></td>
</tr>
<tr>
<td>Telephone consult</td>
<td>9.1%</td>
<td>3.3</td>
<td>€ 35.00</td>
<td>2014 € 111.04              3.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>61.8%</td>
<td>0.1</td>
<td>€ 100.13</td>
<td>2016 € 9.92                3.9</td>
<td></td>
</tr>
<tr>
<td>Out of office hours GP contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes nurse consult</td>
<td>84.5%</td>
<td>3.7</td>
<td>€ 13.25</td>
<td>2008 € 47.54               10</td>
<td></td>
</tr>
<tr>
<td>Specialist visit for DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal medicine (type 1 DM patients)</td>
<td>95.0%</td>
<td>0.6</td>
<td>€ 91.00</td>
<td>2014 € 263.52              8</td>
<td></td>
</tr>
<tr>
<td>Internal medicine (type 2 DM patients)</td>
<td>28.9%</td>
<td>0.7</td>
<td>€ 91.00</td>
<td>2014 € 40.08              8,10</td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>52.0%</td>
<td>0.7</td>
<td>€ 91.00</td>
<td>2014 € 86.54              8,10</td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>15.2%</td>
<td>0.7</td>
<td>€ 91.00</td>
<td>2014 € 9.84               8,10</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>6.4%</td>
<td>0.7</td>
<td>€ 99.00</td>
<td>2014 € 3.86               8,10</td>
<td></td>
</tr>
<tr>
<td>Nephrology</td>
<td>1.8%</td>
<td>0.7</td>
<td>€ 91.00</td>
<td>2014 € 0.17               8,10</td>
<td></td>
</tr>
<tr>
<td>Other specialism</td>
<td>32.8%</td>
<td>1.6</td>
<td>€ 91.00</td>
<td>2014 € 48.52              8,10</td>
<td></td>
</tr>
<tr>
<td>Emergency room visit for DM</td>
<td>0.0%</td>
<td>0.0</td>
<td>€ 259.00</td>
<td>2014 € 0.00               8</td>
<td></td>
</tr>
<tr>
<td>Dietician visit</td>
<td>21.9%</td>
<td>0.9</td>
<td>€ 27.00</td>
<td>2009 € 5.96               10,11</td>
<td></td>
</tr>
<tr>
<td>Podiatrist visit</td>
<td>24.3%</td>
<td>1.2</td>
<td>€ 53.55</td>
<td>2008 € 17.92              10</td>
<td></td>
</tr>
<tr>
<td>Physical therapist visit</td>
<td>21.0%</td>
<td>3.9</td>
<td>€ 33.00</td>
<td>2014 € 27.46              8,10</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation for DM*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day admissions</td>
<td>0.9%</td>
<td></td>
<td>€ 251.00</td>
<td>2009 € 2.43               2,11</td>
<td></td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>1.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days per hospitalisation</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisation cost</td>
<td></td>
<td></td>
<td>€ 476.00</td>
<td>2014 € 38.57              8</td>
<td></td>
</tr>
<tr>
<td>Psychological care for DM**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consult psychologist</td>
<td>4.6%</td>
<td>6.4</td>
<td>€ 64.00</td>
<td>2014 € 19.14              3,8,12</td>
<td></td>
</tr>
<tr>
<td>Elderly care for DM**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DM = diabetes mellitus; GP = general practitioner.
Costs were inflated to 2016 euros using inflation rates published by Statistics Netherlands. "The hospitalisation and day admission rate were calculated by dividing the number of hospitalisations and day admissions in 2012 by the total number of DM patients in 2012."
**Elderly care cost per patient per year for DM were calculated by dividing the total DM elderly care cost (2011 data) by the total number of DM patients in 2011 (Dutch population on 1 January 2011 multiplied with the DM prevalence rate in GP practices [2012 data]).""
### Table B.4. Monitoring/device cost data

<table>
<thead>
<tr>
<th>Resource</th>
<th>% Use*</th>
<th># of prescription per user</th>
<th>Cost per prescription</th>
<th>Cost year</th>
<th>Cost per patient year** (2016 €)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose meter</td>
<td>0.6%</td>
<td>1.1</td>
<td>€ 27.00</td>
<td>2014</td>
<td>€ 0.18</td>
<td>[6]</td>
</tr>
<tr>
<td>Testing strip</td>
<td>34.3%</td>
<td>4.0</td>
<td>€ 82.00</td>
<td>2014</td>
<td>€ 111.82</td>
<td>[6]</td>
</tr>
<tr>
<td>Portable insulin infusions pump</td>
<td>3.2%</td>
<td>9.4</td>
<td>€ 301.00</td>
<td>2014</td>
<td>€ 90.99</td>
<td>[6]</td>
</tr>
<tr>
<td>Finger prick equipment</td>
<td>13.4%</td>
<td>2.6</td>
<td>€ 16.00</td>
<td>2014</td>
<td>€ 5.58</td>
<td>[6]</td>
</tr>
<tr>
<td>Other devices for DM</td>
<td>1.2%</td>
<td>1.0</td>
<td>€ 6.00</td>
<td>2014</td>
<td>€ 0.07</td>
<td>[6]</td>
</tr>
<tr>
<td>Injection pen/syringe</td>
<td>30.2%</td>
<td>4.4</td>
<td>€ 30.00</td>
<td>2014</td>
<td>€ 40.54</td>
<td>[6]</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus.

Costs were inflated to 2016 euros using inflation rates published by Statistics Netherlands.[6]

*The percentage use was calculated by dividing the number of users per resource category by the total numbers of DM medication users, which was assumed to represent the total number of monitoring/device users, due to the lack of data (2014 data).[6]

**As data were only available for DM in total, the costs for T1DM and T2DM separately were derived by applying proportions based on Pharmo/Farminform FiScript data.[7]

### Table B.5. Complication healthcare cost data

<table>
<thead>
<tr>
<th>Complication</th>
<th>Annual probability of event per patient*</th>
<th>% of patients at risk</th>
<th># of events</th>
<th>Unit cost</th>
<th>Cost year</th>
<th>Cost per patient year (2016 €)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>1.4%</td>
<td></td>
<td></td>
<td>€ 5,614.00</td>
<td>2011</td>
<td>€ 82.89</td>
<td>[14,16]</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.6%</td>
<td></td>
<td></td>
<td>€ 18,265.00</td>
<td>2011</td>
<td>€ 116.59</td>
<td>[14,15,17]</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.0%</td>
<td></td>
<td></td>
<td>€ 6,798.00</td>
<td>2011</td>
<td>€ 72.60</td>
<td>[14,15,18]</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.7%</td>
<td></td>
<td></td>
<td>€ 36,657.00</td>
<td>2011</td>
<td>€ 293.59</td>
<td>[14,15,19]</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.2%</td>
<td></td>
<td></td>
<td>€ 16,438.00</td>
<td>2011</td>
<td>€ 29.78</td>
<td>[14,15,20]</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.2%</td>
<td></td>
<td></td>
<td>€ 2,668.00</td>
<td>2011</td>
<td>€ 4.57</td>
<td>[14,15,20]</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>0.7%</td>
<td></td>
<td></td>
<td>€ 63,901.00</td>
<td>2011</td>
<td>€ 512.05</td>
<td>[14,15,20]</td>
</tr>
<tr>
<td>Major hypoglycaemia***</td>
<td></td>
<td>100.0%</td>
<td>0.9</td>
<td>€ 373.00</td>
<td>2011</td>
<td>€ 366.60</td>
<td>Expert opinion, [15,21,22]</td>
</tr>
<tr>
<td>(type 1 DM patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hypoglycaemia***</td>
<td></td>
<td>6.9%</td>
<td>0.1</td>
<td>€ 373.00</td>
<td>2011</td>
<td>€ 2.80</td>
<td>[2-5,7,15,21-23]</td>
</tr>
<tr>
<td>(type 2 DM basal insulin users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hypoglycaemia***</td>
<td></td>
<td>1.3%</td>
<td>0.2</td>
<td>€ 373.00</td>
<td>2011</td>
<td>€ 0.99</td>
<td>[2-5,7,15,21-23]</td>
</tr>
<tr>
<td>(type 2 DM basal/bolus insulin users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hypoglycaemia***</td>
<td></td>
<td>10.1%</td>
<td>0.2</td>
<td>€ 373.00</td>
<td>2011</td>
<td>€ 8.24</td>
<td>[2-5,7,15,21-23]</td>
</tr>
<tr>
<td>(type 2 DM other insulin users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DM = diabetes mellitus.

Costs were inflated to 2016 euros using inflation rates published by Statistics Netherlands.[6]

*The annual probability of a long-term complication event per patient is derived by dividing the rate identified in the study by McEwan et al. by the respective follow-up duration and by applying the weight for low-risk and intermediate-risk patients based on their proportion in the database analysed.[4]

**Assumption made based on expert opinion that all type 1 DM patients use insulin.

***The percentage of type 2 DM patients at risk (e.g. insulin users) was calculated by dividing the number of patients treated with the respective insulin categories by the total number of type 2 DM patients.[5,12,13]
### Table B.6. Indirect cost data

<table>
<thead>
<tr>
<th>Cost item</th>
<th>Units</th>
<th>Unit cost</th>
<th>Cost</th>
<th>Cost per patient year (2016 €)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Productivity losses from paid work</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working age DM patients</td>
<td>43.7%</td>
<td></td>
<td></td>
<td></td>
<td>[3]</td>
</tr>
<tr>
<td>Employment rate</td>
<td>40.0%</td>
<td></td>
<td></td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Percentage taking sick days</td>
<td>62.0%</td>
<td></td>
<td></td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Average # of sick days per year</td>
<td>19.0</td>
<td></td>
<td></td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Working hours per day</td>
<td>8.0</td>
<td></td>
<td></td>
<td></td>
<td>Assumption</td>
</tr>
<tr>
<td>Productivity cost per hour</td>
<td>€ 34.75</td>
<td>2014</td>
<td></td>
<td></td>
<td>[8]</td>
</tr>
<tr>
<td><strong>Lost productivity cost per premature mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM mortality rate</td>
<td>0.3%</td>
<td></td>
<td></td>
<td></td>
<td>Calculation based on [2-4]</td>
</tr>
<tr>
<td>Working age DM patients</td>
<td>43.7%</td>
<td></td>
<td></td>
<td></td>
<td>[3]</td>
</tr>
<tr>
<td>Employment rate</td>
<td>40.0%</td>
<td></td>
<td></td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Full-time equivalent</td>
<td>80.0%</td>
<td></td>
<td></td>
<td></td>
<td>[25]</td>
</tr>
<tr>
<td>Friction period (days)</td>
<td>85.0</td>
<td></td>
<td></td>
<td></td>
<td>[8]</td>
</tr>
<tr>
<td>Working hours per day</td>
<td>8.0</td>
<td></td>
<td></td>
<td></td>
<td>Assumption</td>
</tr>
<tr>
<td>Productivity cost per hour</td>
<td>€ 34.75</td>
<td>2014</td>
<td></td>
<td></td>
<td>[8]</td>
</tr>
<tr>
<td><strong>Welfare payments due to disability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM patients (age 18-64) with disability</td>
<td>27.0%</td>
<td></td>
<td></td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Percentage with complete disability</td>
<td>79.3%</td>
<td></td>
<td></td>
<td></td>
<td>Calculation based on [2]</td>
</tr>
<tr>
<td>Percentage with partial disability</td>
<td>20.7%</td>
<td></td>
<td></td>
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<td>Calculation based on [2]</td>
</tr>
<tr>
<td>Disability level for patients with partial disability</td>
<td>50.0%</td>
<td></td>
<td></td>
<td></td>
<td>Assumption</td>
</tr>
<tr>
<td>Working age DM patients</td>
<td>43.7%</td>
<td></td>
<td></td>
<td></td>
<td>[3]</td>
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<tr>
<td>Modal income</td>
<td></td>
<td>€ 36,500.00</td>
<td>2016</td>
<td></td>
<td>[26]</td>
</tr>
<tr>
<td>Welfare payment % of last salary</td>
<td>70.0%</td>
<td></td>
<td></td>
<td></td>
<td>[27]</td>
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<td><strong>Indirect costs of complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1.4%</td>
<td>€ 1,044.00</td>
<td>2011</td>
<td>€ 15.41</td>
<td>[14-16]</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.6%</td>
<td>€ 8,773.00</td>
<td>2011</td>
<td>€ 56.00</td>
<td>[14,15,28]</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.0%</td>
<td>€ 8,773.00</td>
<td>2011</td>
<td>€ 93.69</td>
<td>[14,15,29]</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.7%</td>
<td>€ 8,773.00</td>
<td>2011</td>
<td>€ 70.26</td>
<td>[14,15,30]</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.2%</td>
<td>€ 6,274.00</td>
<td>2011</td>
<td>€ 11.37</td>
<td>[14-16,31]</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.2%</td>
<td>€ 5,627.00</td>
<td>2011</td>
<td>€ 9.65</td>
<td>[14-16,32]</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>0.7%</td>
<td>€ 5,539.00</td>
<td>2011</td>
<td>€ 44.39</td>
<td>[14-16,33]</td>
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<td>Major hypoglycaemia (type 1 DM patients)</td>
<td>0.9%</td>
<td>€ 50.00</td>
<td>2011</td>
<td>€ 49.14</td>
<td>[Expert opinion, 15,21,22]</td>
</tr>
<tr>
<td>Major hypoglycaemia (type 2 DM basal insulin users)</td>
<td>0.0069%</td>
<td>€ 50.00</td>
<td>2011</td>
<td>0.38</td>
<td>[2-5,7,15,21-23]</td>
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<tr>
<td>Major hypoglycaemia (type 2 DM basal/bolus insulin users)</td>
<td>0.0024%</td>
<td>€ 50.00</td>
<td>2011</td>
<td>0.13</td>
<td>[2-5,7,15,21-23]</td>
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<tr>
<td>Major hypoglycaemia (type 2 DM other insulin users)</td>
<td>0.0202%</td>
<td>€ 50.00</td>
<td>2011</td>
<td>1.10</td>
<td>[2-5,7,15,21-23]</td>
</tr>
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</table>

DM = diabetes mellitus.

Costs were inflated to 2016 euros using inflation rates published by Statistics Netherlands. *

* Units were calculated by multiplying the respective % of patients at risk and # of events, as reported in Table B.5.
REFERENCES FOR APPENDIX

ABSTRACT

Congenital adrenal hyperplasia (CAH) can present as a benign adrenal tumour, which should be treated medically. The diagnosis of CAH must be considered in a patient presenting with adrenal incidentaloma in order to avoid unnecessary adrenalectomy. Urinary steroid profiling is a useful diagnostic tool to identify the presence of CAH.

KEYWORDS

Congenital adrenal hyperplasia, adrenal incidentaloma, urinary steroid profile

INTRODUCTION

An adrenal incidentaloma (AI) is an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease. In radiological series the prevalence is estimated at 2-4% in middle-aged patients, increasing to 10% in 70-year-olds. Guidelines recommend repeated imaging studies to assess the risk of malignancy and biochemical evaluation to identify possible hormonal activity. Adrenalectomy is indicated in case of hormone excess or radiological characteristics suggestive of malignancy.

We present a patient with an AI who initially seemed to meet the criteria for adrenalectomy. Additional analysis, however, revealed an underlying aetiology for which medical treatment was successfully instituted.

CASE REPORT

A 43-year-old male suffered from progressive fatigue and myalgia for more than a year. Evaluation by his general practitioner did not result in a diagnosis. The patient decided to visit a commercial clinic for an MRI scan which revealed a tumour of 5.2 x 4.4 cm in the left adrenal gland. Subsequent analysis elsewhere excluded the presence of hormonal hypersecretion. An unenhanced CT scan was performed, which demonstrated a homogenous lesion in the left adrenal gland with a radiodensity of 19 Hounsfield units and a normal appearing contralateral adrenal gland (figure 1). A ‘wait-and-scan’ strategy was proposed. The patient, however, opted for surgical removal and was referred to our hospital.

His past medical history was uneventful. Besides fatigue and myalgia he reported frequent headaches and night sweats without fever, but had no other complaints. He and his wife were involuntarily childless. He recalled being taller than most of his peers at the age of ten, but ending up as one of the shortest by the end of puberty.
No abnormalities were found at physical examination. He was 1.70 m in height and weighed 69 kg. Laboratory analysis demonstrated a normal complete blood count, electrolytes, glucose, and liver function tests and plasma metanephrines. The results of additional hormone measurements showed: cortisol 350 nmol/l (at 14.00 h), ACTH 27 ng/l (reference range: < 23 ng/l), 17OH-progesterone (17-OHP) 426 nmol/l (4.0-12.0 nmol/l), androstenedione 14 nmol/l (2.6-7.2 nmol/l), DHEAS 3.1 µmol/l (2.7 µmol/l), testosterone 13 nmol/l (16-40 nmol/l), luteinising hormone 3.61 U/l (2.1-11.2 U/l), follicle-stimulating hormone 6.68 U/l (1.8-7.2 U/l), plasma renin activity (PRA) 1.6 nmol/l/h (0.10-2.35 nmol/l/h). Urinary steroid profiling revealed a markedly increased excretion of pregnanediolone, pregnanetriol and pregnanetriolone. Intravenous administration of 250 µg tetracosactide resulted in a peak serum cortisol and 17-OHP of 415 nmol/l and 997 nmol/l, respectively. We diagnosed congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. DNA analysis demonstrated compound heterozygous mutations of the CYP21A2 gene (c.518T>A (p.Ile173Asn) and c.710T>A, c.713T>A, c.719T>A (p.Ile237Asn), (p.Val238Glu), (p.Met240Lys), which are associated with the simple virilising form of classic CAH. Ultrasound examination excluded the presence of testicular adrenal rest tumours. Dexamethasone 0.5 mg once daily was started, resulting in prompt resolution of all his symptoms and biochemical normalisation of the adrenal steroid precursors. The tumour size decreased (4.4 x 2.9 cm) after one year of treatment (figure 1). Dexamethasone was switched to hydrocortisone 10 mg thrice daily with maintenance of excellent clinical and biochemical control.

**DISCUSSION**

We present a patient with a large adrenal tumour caused by newly diagnosed classic CAH due to 21-hydroxylase deficiency (21-OHD). Treatment with glucocorticoids was successful and adrenalectomy was thus avoided. CAH represents a group of autosomal recessive inherited disorders in steroid biosynthesis. Approximately 95% of cases are due to 21-OHD. The most severe form is classic CAH, characterised by adrenal insufficiency with or without aldosterone deficiency (i.e. salt-wasting or simple virilising phenotype, respectively), disorders of sexual development with genital ambiguity in girls, short stature and infertility. Mild 21-OHD results in non-classic CAH, in which genital ambiguity and cortisol deficiency are absent. Patients with non-classic CAH often have manifestations of hyperandrogenism, such as early pubarche, acne, hirsutism or oligomenorrhoea/amenorrhoea. The prevalence of CAH and non-classic CAH is estimated at 1 in 10,000-15,000 and 1 in 500-1000 live births, respectively. Neonatal screening for 21-OHD has been performed in the Netherlands since 2000. Consequently, the risk of missing a diagnosis of classic CAH during childhood is extremely low nowadays. Adrenal tumours have been reported in 11-82% of patients with CAH, the development of which is probably enhanced by prolonged ACTH stimulation of the adrenal cortex. About 45% of these tumours are unilateral, which means that other, as yet unknown, factors contribute to adrenal tumour development in patients with CAH. It has been estimated that among patients with an AI only 0.8% are caused by CAH. This raises the question as to when an underlying diagnosis of CAH should be ruled out. In general, guidelines on AI management recommend adrenalectomy when the diameter of the tumour exceeds 4-6 cm, as the risk of adrenocortical...

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**Figure 1.** CT scan demonstrating an adrenal tumour of 52 mm at presentation. On the right side the same tumour measuring 44 mm after one year of treatment.
carcinoma increases with size. Direct application of this recommendation to our patient would have resulted in an unnecessary adrenalectomy, including the risk of provoking a perioperative Addisonian crisis. Therefore, before adrenalectomy is considered in a patient with AI, the medical history should be checked for symptoms and signs suggestive of CAH such as premature pubarche, short stature and hyperandrogenism. In addition, sex steroids and their precursors (including 17-OHP) should be measured, as recommended by the recent European Society of Endocrinology guideline on AI management as well as the European Society for Medical Oncology guideline on adrenal cancer. High serum levels of 17-OHP are suggestive of CAH, which could be further evaluated by an intravenous tetracosactide stimulation test and, finally, confirmed by genetic analysis. Notably, moderately elevated levels of 17-OHP might also accompany a large adrenal adenoma or an adrenocortical carcinoma. Thus, the specificity of an elevated serum 17-OHP for CAH is limited in the presence of AI.

Urinary steroid profiling (USP) by gas chromatography-mass spectrometry might overcome this problem by demonstrating increased levels of pregnanetriol, pregnanediolone and pregnanetriolone with low levels of cortisol metabolites in a patient with CAH. Another advantage of USP is that it provides a comprehensive evaluation of the steroid biosynthesis which enables detection of not only 21-OHD, but also all other causes of CAH. In addition, recent evidence suggests that USP can distinguish between adrenal adenoma and adrenocortical carcinoma. Thus, USP serves several diagnostic purposes and seems to be a promising first-line test in AI analysis.

In conclusion, adrenal tumours are common in CAH, but CAH as the cause of AI is rare. CAH should be excluded in case of clinical suspicion or when adrenalectomy is considered. Urinary steroid profiling is a useful diagnostic tool in patients presenting with AI.

DISCLOSURES

No conflict of interest declared by the authors.

REFERENCES

First case of severe pneumonic tularemia in an immunocompetent patient in the Netherlands


*Department of Infectious Diseases, Leiden University Medical Center, Leiden, the Netherlands, †Department of Medical Microbiology, Leiden University Medical Center, Leiden, the Netherlands, ‡Department of Pulmonary Medicine, Leiden University Medical Center, Leiden, the Netherlands, §Centre for Infectious Diseases Research, Diagnostics and Screening, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands, ‡National Coordination Communicable Disease Control, Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands, †Department of Bacteriology and Epidemiology, Wageningen Bioveterinary Research, Wageningen, the Netherlands, ‡Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands,

*corresponding author: k.sigaloff@vumc.nl

ABSTRACT

Tularemia is a zoonosis caused by different subspecies of the Gram-negative bacterium Francisella tularensis. We report the first case in the Netherlands of pneumonic tularemia caused by the F. tularensis subspecies holarctica after probable occupational inhalation of contaminated aerosols. Notification of cases of tularemia has been mandatory by law in the Netherlands since 1 November 2016.

KEYWORDS

Tularemia, Francisella tularensis, pneumonia

INTRODUCTION

Francisella tularensis is a Gram-negative intracellular coccobacillus causing tularemia, a bacterial zoonotic disease occurring throughout the northern hemisphere. It has been classified as a potential bioterrorism agent due to its highly infectious and virulent properties. Typically, F. tularensis subspecies tularensis (type A) strains are found in North America and can cause severe systemic disease. By contrast, F. tularensis subspecies holarctica (type B), which is found throughout the northern hemisphere including in Europe, is associated with mild clinical manifestations. In the Netherlands, tularemia re-emerged in 2011. We report the first case of severe pneumonia...
caused by *F. tularensis* subspecies *holartica* (type B) in an immunocompetent patient in the Netherlands.

**CASE REPORT**

A 54-year-old previously healthy gardener was hospitalised after 1 week of progressive influenza-like symptoms including myalgia, fever and a non-productive cough. Physical examination revealed a pulse rate of 90/min, blood pressure of 130/80 mmHg, temperature of 39 °C and oxygen saturation of 88% while breathing ambient air. Breath sounds over the right lung were diminished. Skin and lymph node evaluation produced no abnormal findings. A chest X-ray showed consolidation of the right lower lobe, pleural effusion and a prominent hilus on the right side. Intravenous antibiotic therapy for community acquired pneumonia with penicillin and ciprofloxacin was started. Sputum PCR was negative for *Legionella pneumophila*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*; empirical ciprofloxacin treatment was subsequently stopped. Routine blood and sputum cultures failed to detect a bacterial pathogen. After a few days, the patient’s dyspnoea worsened due to increasing pleural effusion. A computed tomography (CT) scan of the chest showed expansion of the infiltrate, pleural effusion and hilar and mediastinal lymphadenopathy with central necrosis (figure 1). Pleural fluid was obtained and the Gram stain revealed no bacteria. After 4 days, Gram-negative coccobacilli were cultured on chocolate agar from the pleural fluid, which the Maldi-ToF MS identified as *F. tularensis*. Subspecies-specific PCR of the cultured strain confirmed subspecies *holartica* (type B). Antibiotics were switched to gentamicin and ciprofloxacin. A chest drain was inserted for drainage and administration of intrapleural fibrinolytics until culture results were negative. Ciprofloxacin monotherapy was continued for 8 weeks until the patient fully recovered. Assessment of potential exposures to tularemia revealed that the patient had been mowing grass in a greenhouse 3 days before the onset of symptoms. *F. tularensis* could not be isolated from environmental cultures obtained from the greenhouse.

**DISCUSSION**

We report the first case in the Netherlands of pneumonic tularemia caused by *F. tularensis* subspecies *holartica* in an immunocompetent patient after lawn-mowing. This case report illustrates that *F. tularensis* subspecies *holartica* (type B) infection, typically associated with low virulence, can cause severe pneumonia with empyema and necrotising lymphadenitis, and may pose a rare occupational hazard in immunocompetent adults following inhalation of contaminated aerosols. Previous studies report pneumonic tularemia caused by type B *F. tularensis* mainly in immunocompromised patients. One study from Spain describes a cavitary pneumonia due to tularemia in a person without any medical history. Although the subspecies is not mentioned in this case report, it is assumed to be a *holartica* strain due to the geographical location. Tularemia can be transmitted via direct contact with infected animals (i.e. in hunters), arthropod bites, and by ingestion or inhalation. Small rodents, typically hares and rabbits, are considered the key animal reservoir of *F. tularensis*, yet mosquitoes, ticks, and contaminated water or soil are also regarded as a source of human infection. Different clinical manifestations of tularemia are recognised, depending on the portal of entry of bacteria. The ulceroglandular form is most common and combines an inoculation ulcer with regional lymphadenopathy. The oropharyngeal and oculoglandular forms occur after oral or conjunctival contamination, respectively. Pneumonic tularemia follows inhalation of contaminated aerosols. Finally, typhoidal tularemia is a severe systemic disease, irrespective of the portal of entry of bacteria, with high fever and neurological symptoms. The pneumonic and typhoidal forms of tularemia are rare in Europe. Tularemia is endemic in a few European countries including in Scandinavia, where it primarily causes the ulceroglandular form.

Figure 1. Axial CT images demonstrating mediastinal lymphadenopathy (A, arrows), a hilar mass (B), a lobular infiltrate (C) in the right lower lobe and pleural effusion (D). Note the hypodense center of lymphadenopathy (A and B), suggesting central necrosis.

Sigaloff et al. Severe pneumonic tularemia in an immunocompetent patient.
Pneumonic tularemia has been nicknamed lawn mower’s disease and was studied during an outbreak in Martha’s Vineyard (Massachusetts, USA). This case-control study identified lawn mowing and brush cutting as the main risk factors for disease. This implies that *F. tularensis* can persist in the environment and can infect people after being mechanically aerosolised and inhaled. Another outbreak of airborne tularemia was described in Germany, where participants in a hare hunt became infected after rinsing disembowelled hares with a water hose. Clinicians should consider the possibility of tularemia in patients with fever or pneumonia after specific (sometimes occupational) activities that can aerosolise the organism from the environment. However, pneumonic tularemia does not only occur after inhalation; it can also follow the ulceroglandular or typhoidal form of disease. The presence of cutaneous manifestations can differentiate between potential routes of transmission.

The treatment of tularemia depends on the causative subspecies. In North America, for infections with *F. tularensis* subspecies *tularenensis*, aminoglycosides are the antibiotics of choice, followed by doxycycline for less severe cases. In Europe, treatment is often with ciprofloxacin. In our patient, the clinical condition deteriorated after ciprofloxacin, which was included in the initial regimen, was stopped. After the diagnosis of pneumonic tularemia was made, ciprofloxacin was re-started and gentamicin was added, which is recommended in case of systemic disease. Because relapses are described, the duration of antibiotic treatment is often prolonged. In cases with purulent lymphadenitis or empyema there are reports of surgical intervention to reduce the chance of relapse.

After being absent in the Netherlands for almost six decades, tularemia has re-emerged in humans and hares. Since 2011 there have been ten reports of autochthonous human infection, of which four in 2016. Until now, other reported cases had ulceroglandular manifestations either through direct transmission from handling infected hares or through arthropod bites, and possibly through contaminated water or soil. We suspect that our patient contracted tularemia through occupational exposure while cleaning a contaminated area without a protective mask. From November 2016 onwards, clinicians and laboratories are obliged to report all tularemia patients to the local health authorities. This notification and consecutive source tracing will contribute to a better understanding of the burden of disease, the role of existing reservoirs in animals, arthropods and environment, and possible routes of transmission. This information is essential in order to develop effective public health interventions to prevent future infections. Given its rarity, clinical suspicion of tularemia in patients with pneumonia is likely to remain low. However, clinicians should be aware of tularemia, especially in case of specific exposures or failure of empiric antibiotic therapy.

**Acknowledgements**

We thank Corien Swaan (RIVM) for feedback on the final manuscript, and Frans Reuwaat and Maaike de Vries (RIVM) for identification of the isolate. Finally we thank the doctors and nurses in the LUMC who cared for this patient and the staff of the Public Health Services in Leiden for data collection.

**References**

Is nitrous oxide really that joyful?

N.H.P. Glijn1, D. van der Linde1, E. Ertekin2, P.L.M. van Burg2, Y.A.M. Grimbergen2, E.J. Libourel1

1Department of Internal Medicine, Franciscus Hospital, Rotterdam, the Netherlands, 2Department of Neurology, Franciscus Hospital, Rotterdam, the Netherlands, *corresponding author: nhpglijn@gmail.com

ABSTRACT

We present a case of non-immune haemolytic anaemia with leukopenia and acute severe neurological impairments, as a result of severe vitamin B₁₂ deficiency due to recreational use of nitrous oxide.

KEYWORDS

Nitrous oxide, recreational drugs, vitamin B₁₂ deficiency, hemolysis, neurological impairments

INTRODUCTION

There is an increase in the recreational use of nitrous oxide (N₂O) in the Netherlands.1 Users consider the low costs, wide availability, legal status and quick effect as beneficial.1 A balloon is generally used for inhalation and after one inhalation an euphoric effect can be expected. By public opinion, it is considered a relatively safe drug, but is that joyful moment really innocent? We present a 23-year-old woman with recreational N₂O use who presented to our emergency department.

CASE REPORT

This patient, from Yemeni descent, with a previous history of iron deficiency and recurrent venous thromboembolism, presented to our emergency department with acute paresis of her legs and tingling of her limbs. She had no urinary or faecal incontinence. She was not taking any medication, used alcohol socially and mentioned the recreational use of N₂O multiple times daily. On neurological examination, she had symmetrical weakness of the iliopsoas muscle and quadriceps MRC grade 4, paralysis of dorsal flexors of the feet MRC 0, plantar flexors MRC 3, areflexia of the legs and feet, indifferent plantar reflex response, loss of vibration sense from knees to toes and paraesthesia in both legs.

Laboratory analysis revealed a direct antiglobulin test (DAT)-negative haemolytic anaemia: haemoglobin 5.5 mmol/l (7.5-10), leukocytes 1.4 x 10⁹ (4.3-10.0), platelets 266 x 10⁹ (150-400), MCV 98 fl (80-100), vitamin B₁₂ 85 pmol/l (130-700), folic acid 36.6 nmol/l (> 5), homocysteine 120.4 µmol/l (3.6-13.0), and methylmalonic acid 1.10 µmol/l (< 0.45).

Electromyography showed axonal polynueopathy with demyelination. Additional magnetic resonance imaging showed a normal cerebrum and spine. Lumbar puncture revealed no abnormalities in the cerebrospinal fluid, and testing for tuberculosis and polymerase chain reaction for viral infections was negative.

In conclusion, our patient was diagnosed with a non-immune haemolytic anaemia, leukopenia and severe neurological signs as a result of a severe vitamin B₁₂ deficiency due to recreational use of N₂O.

What was known on this topic?

Vitamin B₁₂ deficiency can cause anaemia, leukopenia and neurological signs such as demyelinating myeloneuropathy. The recreational use of nitrous oxide is rapidly increasing, but might not be as innocent as people think. In high daily doses or for a prolonged duration, it has been described to inactivate and deplete vitamin B₁₂.

What does this case add?

This case demonstrates severe symptoms of vitamin B₁₂ deficiency due to nitrous oxide abuse. Thus, in patients with vitamin B₁₂ deficiency, haemolytic anaemia and leukopenia, without an obvious cause at first sight, physicians should be aware of the possibility of nitrous oxide abuse as an underlying cause.
supplements all the laboratory abnormalities gradually normalised but the paraparesis persisted, requiring admission into a rehabilitation centre. After 6 months of intensive physiotherapy and rehabilitation, a slight improvement of the paraparesis has occurred; however, the patient is still only capable of walking within her own home with a walking frame.

DISCUSSION

Vitamin B$_{12}$ deficiency is a common disease with a prevalence of 5-10% in the Dutch population. It is critical to recognise vitamin B$_{12}$ deficiency since it can cause a demyelinating nervous system disease and bone marrow failure. It is associated with a wide variety of signs and symptoms, including macrocytic anaemia, leukopenia, depression, paraesthesia and gait disturbance. Many conditions are known to cause vitamin B$_{12}$ deficiency such as inadequate dietary intake, atrophic gastritis, celiac disease and malabsorption. One of the more unknown causes of vitamin B$_{12}$ deficiency is N$_{2}$O which in the past was used as a relatively safe anaesthetic agent. The recreational use of N$_{2}$O is rapidly increasing, mainly in clubs and festival scenes, as described earlier by Van Amsterdam et al. But nowadays you will also find an increasing amount of discarded N$_{2}$O canisters (whippets) left on the streets by teenagers. In the age of 12-16 years, 8% have used N$_{2}$O and 2% had done so in the past month. The prevalence increases with age, at 16-18 years one out of six students have used N$_{2}$O and 20% had done so in the past month. The Global Drug Survey 2016 reported that 48.3% of the Dutch respondents had ever used N$_{2}$O and 33% had done it recently vs. 38% and 23.7% in the United Kindom. Inhalation of N$_{2}$O reduces anxiety and induces euphoria, with a rapid onset with the peak around one minute after inhaling and then fading after 2 minutes. However, the use of N$_{2}$O is not as innocent as many people think. When N$_{2}$O is used in high daily doses within a short period or for a prolonged duration, it will irreversibly bind, oxidise, inactivate and eventually deplete vitamin B$_{12}$ (figure 1). Several case reports describe vitamin B$_{12}$ deficiency after repetitive use (50-100 bulbs) of N$_{2}$O within 3 hours or heavy use over prolonged time, e.g. more than 10-20 bulbs daily for 10 days. Massey et al. describe a myeloneuropathy secondary to vitamin B$_{12}$ deficiency and Morris et al. describe a progressive lower motor neuronal degeneration despite adequate vitamin B$_{12}$ repletion, suggesting that N$_{2}$O toxicity on motor nerves may be independent of vitamin B$_{12}$-dependent metabolic pathways.

Here we report a young female with severe neurological impairments and haemolysis as a result of vitamin B$_{12}$ deficiency due to recreational use of N$_{2}$O. With the increase in long-term recreational use of N$_{2}$O, physicians should be aware of this unknown cause and specifically ask about N$_{2}$O use when young patients present with vitamin B$_{12}$ deficiency.

CONCLUSION

This case emphasises the serious adverse effects of nitrous oxide abuse. Secondly, we should be aware that there is an increase in the use of N$_{2}$O in the Netherlands.

DISCLOSURES

The authors declare no conflict of interest. No funding or financial support was received.

REFERENCES


Figure 1. Schematic representation of the role of vitamin B$_{12}$ in homocysteine metabolism and the point at which nitrous oxide exerts its effect. This image is reused with permission from Massey et al. Nitrous oxide misuse and vitamin B12 deficiency. BMJ Case Rep. 2016 May 31.

Glijn et al. Vitamin B$_{12}$ deficiency due to nitrous oxide abuse.


Glijn et al. Vitamin B₁₂ deficiency due to nitrous oxide abuse.
A curvilinear sword

B.A. Khan**, S.H. Imam*, S.H. Khan¹, S. Shah¹, D. Chaudhuri²

Departments of ¹Internal Medicine, ²Cardiology, State University of New York Upstate Medical University, New York, United States, *corresponding author: babarkhan43@gmail.com; khanb@upstate.edu

CASE REPORT

An 18-year-old woman presented with a 3-year history of dyspnoea on exertion. Chest X-ray showed right lung hypoplasia with dextroposition of the heart. A CT scan of the chest revealed anomalous venous drainage of the right pulmonary vein into the inferior vena cava (IVC) (figure 1A). Transthoracic echocardiography showed normal sized chambers and normal pulmonary artery pressure with no evidence of an intra-cardiac defect. Two years later, she experienced worsening dyspnoea with significant exercise limitations and recurrent episodes of pneumonia. She could not undergo cardiac MRI due to severe claustrophobia. Subsequently, she had pulmonary angiography, which revealed a scimitar (curvilinear sword shaped) vein from the right lung draining into the supra-diaphragmatic IVC, consistent with the diagnosis of scimitar syndrome (figure 1B). Right cardiac catheterisation demonstrated normal right ventricular (24/2 mmHg) and pulmonary artery (27/10 mmHg) pressures. No intra-cardiac shunt was noticed. She underwent surgical correction and her symptoms improved significantly.

WHAT IS YOUR DIAGNOSIS?

See page 308 for the answer to this photo quiz.

Figure 1. CT scan of the chest (A) and pulmonary angiography (B) showing anomalous venous return and converging branches (short arrows), draining into the IVC (long arrow)
DISCUSSION

Scimitar syndrome, a rare congenital defect, is characterised by partial or complete anomalous pulmonary venous return from the right lung into the systemic venous system. Its presentation varies from asymptomatic state, dyspnoea and recurrent pulmonary infections in adults to severe pulmonary hypertension and heart failure with associated congenital heart defects in infants. The ‘scimitar’ sign, a term meaning curved eastern sword, is a characteristic radiographic finding of a crescent-like shadow in the right lower lung field, due to the anomalous vein. The diagnostic modalities include chest X-ray, cardiac echocardiography, CT, MRI and angiography. Presence of congestive heart failure, recurrent pneumonias, pulmonary/systemic blood flow ratio > 1.5 and pulmonary hypertension warrants surgical correction.

REFERENCES

PHOTO QUIZ

Advanced Waldenström’s macroglobulinaemia presenting as tongue swelling

M. Pentenero, M. Val*, R. Marino, S. Gandolfo

Department of Oncology, Unit of Oral Medicine and Oral Oncology, University of Turin, Turin, Italy,
*corresponding author: matteo.val@outlook.it

CASE REPORT

A 56-year-old female came to our hospital complaining of a relapsing-remitting swelling on the right side of the tongue, dyspnoea and bronchitis not responding to antibiotic therapy. Five years before she had been diagnosed with chronic leucocytosis: blood tests showed hyper-eosinophilia and immunophenotyping of peripheral blood showed positivity of CD3, CD4, CD2, CD7, CD10, CD52, thus suggesting a lymphoproliferative disorder. The patient refused to proceed with further investigations. At admission, due to her past medical history, a bone marrow biopsy, magnetic resonance imaging (MRI) with contrast medium of the head and neck and serum protein electrophoresis were performed. Bone marrow biopsy detected cell monoclonality on a background of polyclonal T-cells, but was not able to identify any neoplasia, while serum protein electrophoresis disclosed a high level of gamma proteins. MRI highlighted three submucosal masses: one of the right body of the tongue, another one in the left anterior part of the tongue and the last one in the right oral vestibule, so that the patient was referred to the oral medicine clinic. Clinical examination just revealed an asymptomatic swelling of about 2-3 cm in diameter involving the right side of the tongue with an overlying healthy mucosa and a doughy consistency. An incisional biopsy confirmed the presence of a soft yellowish mass infiltrating the tongue (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 310 for the answer to this photo quiz.
ANSWER

The past medical history was suggestive for oral manifestation of a lymphoproliferative disorder, with the first hypothesis a deposit of amyloid. Plain macroGLOSSIA is a common sign of primary amyloidosis, while an increased volume with multiple nodules may be found in dialysis-related amyloidosis. In fact, macroGLOSSIA has been claimed to be a potential paraneoplastic sign of plasma cell dysCRASia. Nevertheless, in the present case bone marrow biopsy failed to identify any specific haematological disorder. When addressing other potential diagnoses, the absence of symptoms and the persistency of the relapsing-remitting tongue swelling over several weeks lead to the exclusion of an acute inflammatory/infective disorder (e.g. tongue abscess). Other disorders to be excluded in case of relapsing-remitting tongue swelling over time were a false lingual artery, tuberculosis, syphilitic gumma, actinomycosis and infiltrating carcinoma.

The pathological assessment of the oral biopsy showed mature B-cells (CD20+, CD3-, CD4-, CD5-, CD7-, CD8-, CD138-) with secretory capacity with stacks formed of kappa chains (figure 2). The joint assessment of such results, bone marrow biopsy and serum protein electrophoresis resulted in the diagnosis of Waldenstrom’s macrogLOBULINAEMIA with oral secondary manifestations. Two weeks after the diagnosis the patient died of a cardiac arrest. Death occurred because of direct damage to the heart and lung tissue due to massive deposition of M-protein and lymphocyte invasion, with a pathological appearance similar to what was observed in the tongue biopsy.

Oral manifestations of Waldenstrom’s macrogLOBULINAEMIA have been reported in just two patients, both of whom had gingival hyperplasia, in one case preceding the onset of massive oral ulcers. Oral manifestations of Waldenstrom’s macrogLOBULINAEMIA have been reported in just two patients, both of whom had gingival hyperplasia, in one case preceding the onset of massive oral ulcers.

The present case reinforces the previously reported importance of an exhaustive assessment of macroGLOSSIA as a potential sign of haematological disorders.

REFERENCES


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LETTER TO THE EDITOR

The association between glucose variability and mortality

S. Eslami1,2,*, R. van Hooijdonk3, F. van Braam Houckgeest4, J.P. van der Sluijs5, P.E. Spronk6,7, M.J Schultz3,7,8, A. Abu-Hanna1 for the Tight Glucose Control Group Investigators

Increased blood glucose variability has been associated with higher mortality in critically ill patients, and was therefore proposed as a quality measure of glucose control in the intensive care unit (ICU).1-5 However, most studies related to glucose variability have not adjusted for potential confounders of this association, such as the presence of blood glucose control, the frequency with which glucose is measured, and the severity of illness.6

We hypothesised an independent association between the blood glucose level and hospital mortality, even when adjusting for such potential confounders. This study comprises a secondary analysis of an earlier completed implementation project of a glucose control guideline.7 The glucose variability was measured for patients from three mixed medical-surgical ICUs during two periods: one year before and one year after the implementation of the new glucose control guideline. This new guideline aimed at a blood glucose target range of 80 - 110 mg/dl, instead of the glucose level < 150 mg/dl in the before period, and required more frequent glucose measurements.7,8

Patient data were extracted from the National Intensive Care Evaluation (NICE) registry. Readmitted patients, those spending less than 24 hours on the ICU, and patients with less than three glucose measurements were excluded from the present analysis.

For blood glucose variability, we used three common measures: the standard deviation of the glucose levels, the mean absolute glucose, and the mean amplitude of glycaemic excursions (MAGE).1 We selected three widely used measures of the quality of blood glucose control: mean blood glucose level, the frequency of glucose measurements, and the incidence of severe hypoglycaemia (defined as a glucose < 40 mg/dl).

We used univariate and multivariate logistic regression analysis to estimate and test the association between measures of glucose variability and hospital mortality. The multivariate logistic regression analysis for each measure of glucose variability included the variables that were suggested as confounders as they meet the criteria for confounding: severity of illness (expressed as APACHE II score); the overall blood glucose level (expressed as the mean blood glucose of the entire stay of the patient in the ICU); blood glucose measurement frequency (expressed as the mean interval between measurements); having at least one severe hypoglycaemia event (< 40 mg/dl blood glucose level); and the specific ICU.

A total of 2175 patients met the inclusion criteria: 1132 admitted before and 1043 after implementation of a new guideline for glucose control. Standard deviation and mean absolute glucose, but not MAGE, increased significantly after implementation of the new guideline.

Results of the univariate/multivariate analysis are shown in table 1. All measures of glucose variability were associated with hospital mortality in the univariate analysis. After adjustment has been made for all covariates including admission type, the period (before/after implementation), APACHE score, measurement interval, mean BGL, severe hypoglycaemia, hospital, and interaction between hospital and mean BGL, the multivariate analysis showed that none of the glucose variability measures were independently associated with hospital mortality. The result did not change when we stratified patients into medical and surgical patients (data not shown).

Our findings stand in contrast to previous studies, which reported on an independent association of measures of glucose variability with mortality.1-5 One possible
explanation for the discrepancies is that the other studies did not adjust for all identified confounders. We had the unique opportunity to do that by investigating the behaviour of measures of glucose variability and their association with hospital mortality in a multicentre study before and after the implementation of a new blood glucose control guideline.

Our findings show that comparison among study results on measures of glucose variability is difficult and requires accounting for various confounders including the presence of a blood glucose control regime, severity of illness, overall glucose level and measurement frequency.

**Table 1. Univariate and multivariate logistic regression analysis for hospital mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95 % CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>SD</td>
<td>1.00 (1.00 - 1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAG</td>
<td>1.04 (1.03 - 1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAGE</td>
<td>1.00 (1.00 - 1.01)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Adjustment has been made for admission type, before/after implementation, APACHE score, measurement interval, mean blood glucose, severe hypoglycaemia, hospitals and interaction between hospitals and mean blood glucose. There was no considerable collinearity between indicators of blood glucose variability and other independent variables. SD = standard deviation, MAG = mean absolute glucose, MAGE = mean amplitude of glycaemic excursions.

**REFERENCES**