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Early prediction and detecting of type 2 diabetes and related complications

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DOI (link to publication from Publisher):
10.5278/VBN.PHD.MED.00067

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

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EARLY PREDICTION AND DETECTING OF TYPE 2 DIABETES AND RELATED COMPLICATIONS

BY
SIMON LEBECH CICHOSZ

DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

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by

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Dissertation submitted

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PhD Series:	Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-761-4

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2016

CV

I have a M.Sc. in Biomedical Engineering and Informatics (BMEI) from Aalborg University. BMEI is an education that combines engineering with knowledge of biology and medicine. It is an exciting interdisciplinary education that makes it possible to collaborate with physicians and other clinical professionals in the development and implementation of new technologies within the healthcare sector.

I have an innovative and research oriented approach for new ways to improve diagnosis and treatment, as well as improving the efficiency of existing business processes within the healthcare service. Throughout my work as a student and later as a PhD Fellow I had the opportunity to work with many different aspects; innovation and patenting of new technology; supervision and examination of several master students; business development and innovation in collaboration with companies, research institutions and interest organizations; research in COPD and Diabetes along with the publishing of over 20 scientific contributions in the form of journal articles and abstracts.

PUBLICATIONS IN THE PHD THESIS

Cichosz, Simon Lebech; Dencker Johansen, Mette; Hejlesen, Ole K. **Toward Big Data Analytics: Review of Predictive Models in Management of Diabetes and Its Complications**. Diabetes science technology, 2016

Cichosz, Simon Lebech; Dencker Johansen, Mette; Ejskjaer, Niels; Hansen, Troels Krarup; Hejlesen, Ole K**. Improved Diabetes Screening Using an Extended Predictive Feature Search**. Diabetes Technology and Therapeutics, 2014

Cichosz, Simon Lebech; Dencker Johansen, Mette; Ejskjaer, Niels; Hansen, Troels Krarup; Hejlesen, Ole K. **A Novel Model Enhances HbA1c-based Diabetes Screening Using Simple Anthropometric, Anamnestic, and Demographic Information**. Journal of Diabetes, 2014

Cichosz, Simon Lebech; Louise Lundby Christensen; Mette Dencker; Lise Tarnow; Thomas Peter Almdal; Ole K. Hejlesen; The CIMT Trial group **Prediction of Excessive Weight Gain In Insulin Treated Patients with Type 2 Diabetes**. Journal of Diabetes, 2016

RELATED PUBLICATION BY THE AUTHOR

Riis, Hans Christian; Jensen, Morten Hasselstrøm; Cichosz, Simon Lebech; Hejlesen, Ole**. Prediction of exacerbation onset in chronic obstructive pulmonary disease patients**. Journal of Medical Engineering & Technology, 2016

Fleischer, Jesper; Lebech Cichosz, Simon; Hoeyem, Pernille; Laugesen, Esben; Loegstrup Poulsen, Per; Sandahl Christiansen, Jens; Tarnow, Lise; Krarup Hansen, Troels. **Glycemic Variability Is Associated With Reduced Cardiac Autonomic Modulation in Women With Type 2 Diabetes**. Diabetes care, 2015

Cichosz, Simon Lebech; Dencker, Mette; Knudsen, Søren Tang; Hansen, Troels Krakrup; Ole K. Hejlesen; **A classification model for predicting eye disease in newly diagnosed people with Type 2 diabetes**. Diabetes Research and Clinical Practice 2015

Cichosz, Simon Lebech; Frystyk, Jan, Ole K. Hejlesen; Tarnow, Lise; Fleischer, Jesper; **A Novel Algorithm for Prediction and Detection of Hypoglycemia Based on Continuous Glucose Monitoring and Heart Rate Variability in Patients With Type 1 Diabetes**. Journal of Diabetes Science and Technology 2014

Christensen TF; Cichosz SL; Tarnow L; Randløv J; Kristensen LE; Struijk JJ; Eldrup E; Hejlesen OK. **Hypoglycaemia and QT interval prolongation in type 1 diabetes – bridging the gap between clamp studies and spontaneous episodes**. J Diabetes Complications. 2014

Cichosz, Simon Lebech; Frystyk, Jan; Tarnow, Lise; Fleischer, Jesper. **Combining Information of Autonomic Modulation and CGM Measurements Enables Prediction and Improves Detection of Spontaneous Hypoglycemic Events**. Journal of Diabetes Science and Technology, 2014

Cichosz, Simon Lebech; Fleischer, Jesper; Hoeyem, Pernille; Laugesen, Esben; Poulsen, Per Loegstrup; Christiansen, Jens Sandahl; Ejskjaer, Niels; Hansen, Troels Krarup. **Assessment of postprandial glucose excursions throughout the day in newly diagnosed Type 2 diabetes**. Diabetes Technology & Therapeutic, 2013

Cichosz, S L; Fleischer, J; Hoeyem, P; Laugesen, E; Poulsen, P L; Christiansen, J S; Ejskjær, N; Hansen, T K. **Objective measurements of activity patterns in people with newly diagnosed Type 2 diabetes demonstrate a sedentary lifestyle**. Diabetic Medicine, 2013

Morten H Jensen, Simon L Cichosz, Birthe Dinesen and Ole K Hejlesen. **Moving prediction of exacerbation in chronic obstructive pulmonary disease for patients in telecare**. Journal of Telemedicine and Telecare 2012

ENGLISH SUMMARY

Diabetes is a frequent metabolic disorder defined by chronic hyperglycemia which is caused by a deficiency in the endocrine system. Detection of Type 2 diabetes and related complications are important in starting the proper treatment as early as possible because long-term complications take years to develop. Therefore, early treatment can delay or minimize these complications. One of the challenges is to find these patients before they develop serious complications. When patients are diagnosed with Type 2 diabetes, it is a challenge to identify, which patients will develop a specific complication. Diabetes affects most organs of the body - from the small blood vessels to the larger macro structures such as the heart. Patients may therefore get complications on both cognitive function, extremities, heart, kidney, eyes, etc. Targeting of treatment may be an important means to achieve the best possible individual treatment effects. Predictive models have the potential to help in diagnosing patients and targeting proper treatment.

The PhD thesis summarizes the general use of predictive models in diabetes and focus on two main areas in the use of predictive models within Type 2 diabetes.

The first part is concerning the diagnosis of latent diabetes in the common population using several types of screening approaches. The studies show that using predictive models help identify people with diabetes at an early stage. Our findings suggest that additional information could be used to increase the performance of such screening models. An extended feature search might also increase the performance compared to the more traditional developing of such models.

The second part described in the thesis revolves around predicting which patients using insulin would be prone to large weight gains as a result of the treatment. The study show how the rate of weight change is highly associated with the weight change one and a half years later. Using our proposed model, the physician could screen the patient and identify a group with high incidence of excessive weight gain. The next step is to validate the models and investigate the impact of using these in a clinical setting.

DANSK RESUME

Diabetes er en hyppig metabolisk lidelse defineret ved kronisk hyperglykæmi, der er forårsaget af en defekt i det endokrine system. Diagnostik af Type 2-diabetes og de relaterede komplikationer er vigtige at identificere for at starte den rette behandling så tidligt som muligt, idet langsigtede komplikationer tager år at udvikle. Det er derfor hensigtsmæssigt med tidlig behandling, da det kan forsinke eller minimere disse komplikationer væsentligt. En af udfordringerne er at opspore disse patienter, før de udvikler alvorlige komplikationer. Når patienter er diagnosticeret med Type 2-diabetes, er det en udfordring at vide hvilke patienter, der vil udvikle hvilke komplikationer. Diabetes påvirker de fleste af kroppens organer, herunder ekstremiteter, hjerte, nyrer, øjne, kognitive funktion, med videre. Målretning af behandling kan være et vigtigt middel til at opnå de bedst mulige individuelle behandlingseffekter. Prædiktive modeller har potentiale til at styrke diagnosticering og målretning af behandlingen.

Ph.d.-afhandlingen opsummerer forskning af prædiktive modeller i diabetes og fokuserer på to hovedområder i brugen af prognostiske modeller i Type 2-diabetes.

Den første del omhandler opsporing af latent diabetes i befolkningen ved hjælp af flere typer screeningsmetoder. Studierne viser, at anvendelse af prædiktive modeller kan hjælpe med at identificere diabetikere i en tidlig fase. Resultaterne fra studierne tyder på, at yderligere oplysninger omkring patienten der ofte ikke anvendes i udviklingen af disse modeller, kan bruges til at øge effektiviteten af sådanne screeningsmodeller. En udvidet featuresøgning kan ligeledes øge effekten i forhold til de mere traditionelle metoder.

Den anden del, beskrevet i denne afhandling, omhandler prædiktion af patienter, der er tilbøjelige til store vægtforøgelse som følge af insulin-behandlingen. Studiet viser, hvordan hastigheden af vægtændring de første måneder er forbundet med vægtændringer halvandet år senere. Ved hjælp af vores foreslåede model, kan læger screene patienter og identificere en patientgruppe med risiko for høj vægtstigning. Et

fremtidigt skridt vil være at validere modellerne og undersøge konsekvenserne af at bruge disse i klinisk praksis.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my gratitude to all the people who made it possible for me to work on this very interesting project.

I wish to express my most sincere gratitude to Ole Kristian Hejlesen for introducing me to research, the field of diabetes and the art of modelling, particularly machine learning and for the fantastic support during my PhD study. I first met Ole in 2008 as he co-supervised my 5th semester project. I would also like to send a grateful thanks to my other supervisor, Mette Dencker Johansen, for guiding me in many aspects during my PhD.

My thanks go to all my great colleagues at Aalborg University and Aarhus University, who were always there to help me when I needed them.

ABBREVATIONS

ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AUC	Area under the curve
BG	Blood glucose
BMI	Body Mass Index
CGM	Continuous glucose monitoring
CIMT	Copenhagen Insulin and Metformin Therapy Trial
DCCT	Diabetes Control and Complications Trial
EEG	Electroencephalography
FPG	Fasting blood glucose
HbA1c	Hemoglobin A1c
NHANES	National Health and Nutrition Examination Survey
NPV	negative predictive value
OGTT	Oral glucose tolerance test
PG	Plasma glucose
PPV	positive predictive value
ROC	Receiver operating characteristics curve
SMBG	Self-monitoring of blood glucose
SVM	support vector machine
UKPDS	United Kingdom Prospective Diabetes Study

TABLE OF CONTENTS

INTRODUCTION

Diabetes is a frequent metabolic disorder defined by chronic hyperglycemia which is caused by a deficiency in the endocrine system[1]. The disease is a major cause of morbidity as well as premature mortality because of long-term complications such as cardiovascular disease, blindness, kidney failure, and amputations [2–4]. With early diagnosis and subsequent lifelong good glycemic control and early treatment of complications – the patient with diabetes can have a good life quality and reduce the risk of complications that compromise their well-being [1].

Early diagnosis of Type 2 diabetes is thus very important as intensive diabetes control can reduce long-term complications [5–7]. Emerging technologies such as predictive models have the potential to improve the diagnostics and treatment of patients [8]. This thesis presents an overview of research in this area of predictive models within diabetes and the related complications. Furthermore, the thesis focus on two main areas in the use of predictive models within Type 2 diabetes.

BACKGROUND

The following section gives an understanding of the chronic disease diabetes, existing diagnostic methods, an introduction to the most common complications related to diabetes, and how these complications typically are treated. Furthermore, the section contains an introduction to predictive modeling and how these mathematical models can be used to diagnose and design specialized treatment plans.

PREVALENCE

In Denmark, approximately 320,000 people have diabetes [9]. Furthermore, it is estimated that for every three persons diagnosed with Type 2 diabetes two persons have undiagnosed diabetes. The majority of people suffering from diabetes under age 25 have Type 1 diabetes, while the vast majority of people suffering from diabetes over 25 years have Type 2 diabetes.

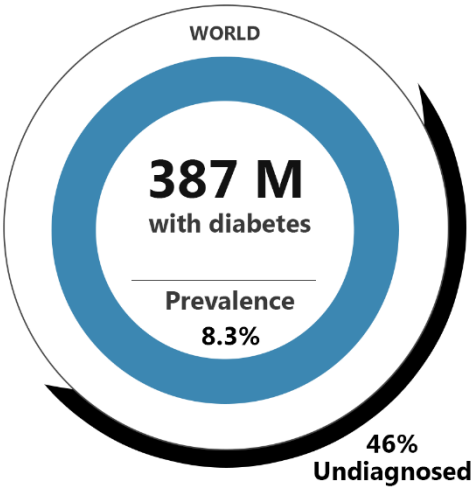

Figure 1 – undiagnosed percentage of people with diabetes

The prevalence of Type 1 and Type 2 diabetes is increasing, but the number of people suffering from Type 2 diabetes is rising much faster due to increasing lifetime of the population and the obesity epidemic [10]. The disease is associated with increased morbidity, increased mortality, and increased healthcare costs [10]. Danish and foreign studies show that ~7% of the total health service budget is used to treat diabetes and complications affecting the kidneys, eyes, and cardiovascular system [11].

In 2010, the prevalence of Type 2 diabetes in the United Kingdom, United States (U.S.), China and the United Arab Emirates ranged from 7% to 34% of the population [12,13]. Approximately 7 million people have undiagnosed diabetes in U.S. and when finally diagnosed, up to 30% show clinical manifestations of diabetic complications [14]. Worldwide, it is estimated that approximately 350 million people will be diagnosed with diabetes in 2025. The primary growth will occur in developing countries.

DIABETES

Diabetes is defined by chronic hyperglycemia caused by one or more underlying causes. Some of these causes diabetes by a direct effect on beta cell function or by interfering with the effect of insulin in the peripheral tissues. In other cases, diabetes is part of a more generalized impact of several organs or organ systems.

There are mainly two types of diabetes; Type 1 and Type 2 Diabetes. Diabetes occurs when the body cannot produce enough of the hormone insulin or uses insulin ineffectively (figure 2). Insulin works as a gatekeeper to let the cell's membrane absorb glucose and uses it as an energy source. Because of an autoimmune process with very sudden onset, people with Type 1 diabetes lose their ability to produce adequate amounts of insulin and therefore need insulin therapy to survive. On the other hand, people with Type 2 diabetes can be overlooked and stay undiagnosed for years. People with Type 2 diabetes lose their ability to use insulin gradually during years. Those who are affected by Type 2 diabetes are often unaware of the long-term complications. [15,16]

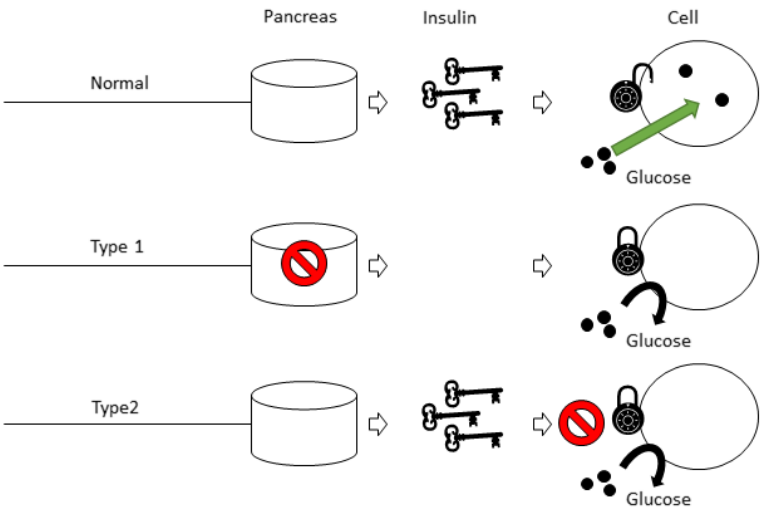

Figure 2 - a graphical illustration of the differences between a normal person, one with type 1 diabetes and one with Type 2/gestational diabetes.

TYPE 1 DIABETES

Type 1 diabetes is characterized by a lack of insulin production due to problems related to the beta-cells in the islets of the Langerhans in the pancreas. In most cases, the underlying mechanism is an immune response targeting the islets [17]. This response is caused by a combination of congenital genetic disposition and dispositions evoked by environmental factors. Type 1 diabetes occurs much more frequently in patients with other autoimmune diseases, such as celiac disease, Addison's disease, and Thyroid diseases. If there is a family history of any of these diseases, the risk for Type 1 diabetes is higher. The development is gradual, but the clinical onset is often acute.

TYPE 2 DIABETES

Type 2 diabetes is a complex heterogeneous condition in which the more recent genetic studies have revealed several subcategories [15]. Type 2 diabetes is a result of an interaction between genetic predisposition and environmental factors - particularly

physical inactivity and obesity. Excess abdominal fat distribution and obesity (BMI> 30 kg / m 2) have explained the majority of cases of Type 2 diabetes. In children and adolescents, with light hyperglycemia, there will often be diagnostic problems since they might have a slow progression in type 1 diabetes. This condition may later become insulin-dependent. Nevertheless, because of the increasing incidence of obesity the prevalence of children and adolescents with Type 2 diabetes is also growing, particularly among ethnic minorities [10]. Type 2 diabetes typically occurs after the age of 40, but may also occur before. The average age at diagnosis for Type 2 diabetes in Denmark is approximately 55 years. Approximately 5% of the Danish population suffers from diabetes, from which 80-90% of these are diagnosed with Type 2 diabetes and more than half of these are older than 65 years. [15]

DIAGNOSTIC OF DIABETES

The symptoms of diabetes are: excessive thirst, large frequent urination, unintentional weight loss, recurrent infections. Diabetes can be diagnosed by evaluating glycated hemoglobin (HbA1c) taken from a blood sample. If the HbA1c reveals ≥48 mmol/mol (6.5%) the diagnosis can be suspected. However, the diagnosis must be confirmed by another sample.

HbA1c is used for both diagnosis and monitoring of diabetes. HbA1c reflects a patient's mean plasma glucose over a longer period - approximately 3 months - since HbA1c glycation is a function of the concentration level of plasma glucose. Previously glucose tolerance test (OGTT) or fasting blood glucose (FPG) were used to diagnose diabetes [18]. This is out phased because of a number of benefits from the use of HbA1c such as: the HbA1c assay is now standardized, analytical and biological variability is modest, fasting is unnecessary, and the association of cardiovascular disease is better for HbA1c than FPG. [19]

However, the HbA1c assay is not without limitations. For certain groups of patients,

the HbA1c cannot be used for diagnostic or at least uncertainties need to be incorporated. These are conditions, in which the erythrocyte's life is affected. Furthermore, despite many advantages of using the HbA1c assay. The sensitivity of the HbA1c for finding latent diabetes, such as for screening purposes, may not be as sensitive compared to OGTT [19–23].

SCREENING FOR DIABETES

Type 2 diabetes have a long latent period. Screening for diabetes can be a means for early diagnosis of Type 2 diabetes. However, screening program is only used in few places. Before starting a screening process, the World Health Organization (WHO) has outlined 10 sensible criteria which have to be meet. These are as follows: [24].

1. The condition sought should be an important health problem.

2. There should be an accepted treatment for patients with the recognized disease.

3. Facilities for diagnosis and treatment should be available.

4. There should be a recognizable latent or early symptomatic stage.

5. There should be a suitable test or examination.

6. The test should be acceptable to the population.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

8. There should be an agreed policy on whom to treat as patients.

9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

10. Case-finding should be a continuing process and not a “once and for all” project.

Type 2 diabetes meets most of these criteria. Screening the entire population is not cost-effective, therefore priority in the screening process must rely on choosing people at high risk of Type 2 diabetes [25,26]. Numerous studies of diabetes screening have been published during the last decade [12,27]. Risk prediction or risk stratification models have a considerable potential to be applied in a screening context in order to identify high risk individuals who should subsequently undergo testing for diabetes [12,27].

TREATMENT OF DIABETES

The treatment of diabetes is a multidisciplinary challenge which include physicians, nurses, general practitioners, social workers and nutritionists. In the management, key goals are often as follows[28]:

1. Lowering the HbA1c.

2. Avoiding episodes of hypoglycemia.

3. Prevention, early diagnosis, and effective treatment of complications.

4. Treatment of hypertension.

5. Control of other risk factors related to cardiac diseases.

6. Postprandial targeting.

7. Relief of symptoms.

8. Minimal injection frequency.

Treatment of Type 2 diabetes mainly consists of a combination of lifestyle intervention and pharmacological treatment. There is evidence that early and

effective treatment programs are important for the prognosis of Type 2 diabetes and all patients, especially newly diagnosed, should be offered early pharmacologic treatment and interventions to improve lifestyle [29]. Lifestyle intervention or non-pharmacological treatment consists of disease-specific patient education; knowledge and skills about the disease; self-care; dietary treatment; consulting for physical activity; smoking cessation [29].

Type 2 diabetic patients are at high risk of having or developing early cardiovascular disease and intensive treatment of all risk factors and smoking cessation is therefore important. Pharmacological treatment for hypertension often involve administration of angiotension-converting enzyme (ACE) inhibitor [29].

The medical treatment used to regulate the blood glucose level often consists of metformin as a starting point, though many patients are eventually treated with insulin to reach the therapeutic targets. The strength of using metformin is that it is effective in lowering HbA1c and makes a minimal risk of hypoglycemia and weight gain. In addition to that Metformin is also easy to use and the related costs are low.[29] Insulin is used when treatment goals are not achieved with diet, exercise and oral medication. Especially younger patients with Type 2 diabetes will eventually require insulin, but also many elderly patients will eventually need additional insulin therapy. Insulin has two main effects. First, insulin stimulates the cells to absorb glucose from the bloodstream, in order to lower the blood glucose level. Inside the cells, the glucose may be used as "fuel" for the cell's many functions, or it may be stored as glycogen. The second major effect of insulin stimulates the hepatic production of glucose from the stored glycogen in the liver. When blood glucose is high and the amount of insulin in the blood increases, the insulin inhibitor the hepatic release of glucose. In contrast, when blood glucose is low and the amount of insulin drops, the liver's release of glucose increases. Insulin is however not without adverse effects. Insulin increases the incident of hypoglycemia and contribute to weight gain in some patients. The psychological barrier associated with insulin treatment and the accompanying weight gain can affect compliance and diabetic control. [30]

DIABETES COMPLICATIONS

Early mortality among diabetes patients continues to be much more frequent compared to the rest of the population. This is significantly influenced by the presence of late diabetic complications, such as diabetic nephropathy, retinopathy, neuropathy, and arteriosclerosis [31]. Diabetes is a condition with substantial increased risk of late complications. This risk of getting late diabetic complications increases if the treatment is insufficient and the person with diabetes has a high blood glucose level, high blood pressure, and high cholesterol. Late complications are caused by damage to blood vessels and nerves. Insufficient diabetes control leads to narrowing and constrictions in the small blood vessels of the body These strictures leads to damage to the eyes, kidneys, nerves, feet, brain and heart. [29]

Table 1 – Late diabetic changes and complications

Changes			
Neurological		*Vascular*	
Sensomotoric neuropathy	Autonomic neuropathy	Macroangiopathy	Microangiopathy
Distal extremities	Blood pressure Regulating vessels Bladder Intestine Sexual function	Lower extremity Neck Brain Coronary arteries	Kidney glomeruli Retina Myocardium

Diabetic retinopathy is considered as the most common complication among the late diabetic complications. The incidence of diabetic retinopathy is approximately 10,000 cases of blindness every year in the U.S. [32]. The risk of developing diabetic retinopathy or other microvascular complications depends on the duration and the

degree of hyperglycemia, and hypertension [32]. Diabetic nephropathy is the leading cause of renal failure. The cause of diabetic nephropathy is not well understood, however it is assumed that the underlying mechanisms are the same as for other microvascular complications [33]. The time a person is diagnosed with Type 2 diabetes, approximately 7 % already suffer from nephropathy. Diabetic neuropathy is a type of nerve damage that commonly occur when having diabetes. Hyperglycemia can injure the nerve fibers throughout the body. However, diabetic neuropathy most often damages the nerves in the distal body parts such as hands and feet. The prevalence of diabetic neuropathy rely on the duration of the having the disease and approximately 50 percent of patients with diabetes will develop neuropathy [34].

STATISTICAL EVENT PREDICTION AND DETECTION

Predictive modelling uses statistics to predict outcomes. Predictive modelling can be applied to any type of unknown event, regardless of when it occurred. In practice, this is often the art of separating different situations from each other as illustrated in figure 3. [35]

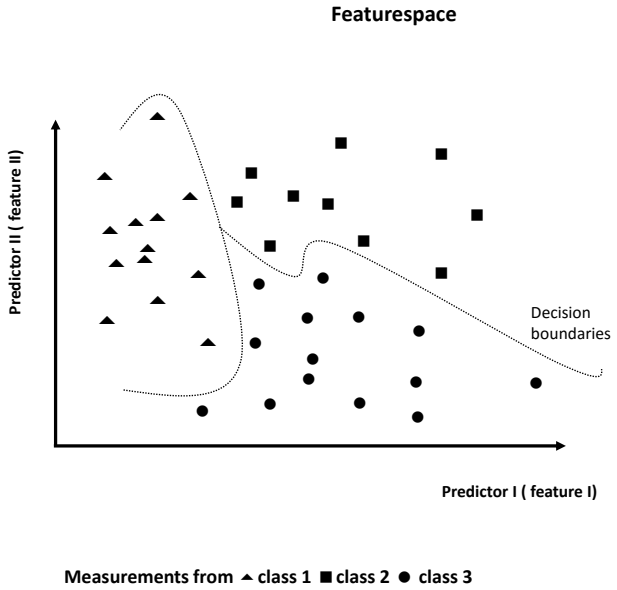

Figure 3 – illustrating the case of separating three classes using a decision boundary with two predictors/features.

In a medical context, these methods have the potential to combine different types of information: from anthropometric, anamnestic, demographic, and biomarkers. The combined information of the patient might help in either a diagnostic result or a prognostic result [36]. In clinical practice, a physician typically also use many of these information to diagnose a patient. The doctor asks the patient questions about

lifestyle, perhaps takes an ECG of the patient, and order a series of blood samples to test for several biomarkers. The combined amount of information would then make up the conclusion or create a working hypothesis about the patient´s health [37]. The interplay between different risk markers is complex and very hard to calculate by the human brain. For example, obesity is a well-known risk marker for diabetes, the same goes for smoking, and lack of exercise, but the combined risk is harder to estimate. Using predictive models makes it possible to combine the information in a systematic manner andproduce reliable results if used correctly [36]. The result can help the physicians and other clinical staff making specialized treatment plans and estimating the prognosis of the specific patient.

Modelling approach

Developing a prediction model requires several components as seen in figure 4 [38]. In the following section, this process will be described in a structured manner.

First, data needs to be acquired from the real world; hereafter noise and outliers must be removed before the data can be modelled. Finding and selecting relevant features is one of the most important components in a successful prediction model [38]. This also leads back to the data acquisition.

If the features or measurements do not contain relevant information about the event, the final model will not be successful. The features extraction can be explained as the transformation of information to something readable by the computer – e.g. features from an ECG could be pulse or premature beats which is a mathematical transformation from the original signal. It is not required that the feature is mathematically derived from the original information, e.g. age or gender are often used as a feature in a predictive model.

The next component is training the chosen model - this is often done by searching for the best decision boundary separating the classes (figure 4). The last component is to evaluate the model by testing it on new patient not used for training the model. This is extremely important to ensure that the model is general and not just fitted to our sample of training subjects [39].

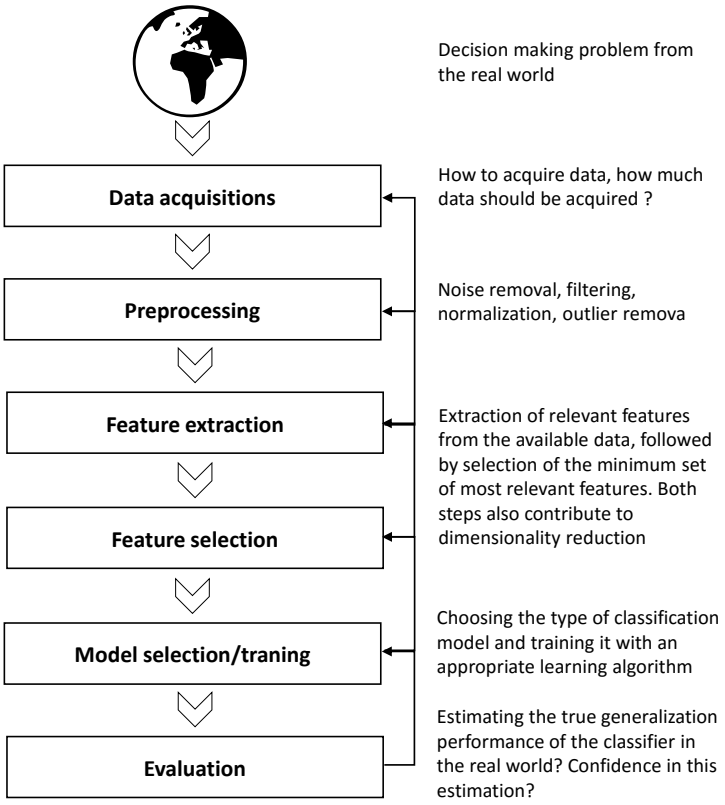

Figure 4 – illustration of the components in developing a predictive model.

AIMS OF STUDIES

Summary

Diabetes is one of the leading causes of morbidities worldwide and half of the group of people suffering from diabetes do not know they suffer from it. Early diagnosis of diabetes is important because it can help to reduce and slow the progression of the complications. When received the diabetes diagnosis, it is crucial to target the right patient for the right treatment. Predictive models contribute to potentially help diagnosing people and targeting the right treatment on an individualized level.

Study I

The aim of study I was to review and present the literature on predictive models in screening for and the management of prevalent short- and long-term complications in diabetes.

Study II

Screening for diabetes thought to be a key factor for early diagnosis and treatment and hereby decrease the risk of late diabetic complication. We investigated the feasibility and performance of a model based on extended predictive features and compared it with two widely accepted models. The aim was to explore the possibility of developing a simple and accurate question based model for the use in screening for Type 2 diabetes.

Study III

Sensitivity of glycated hemoglobin (HbA1c) is not optimal in screening for patients with latent diabetes. The hypothesis of the study was that simple healthcare information would lead to improved accuracy. The aim was to improve methods for diabetes screening by using data from the National Health and Nutrition Examination Survey (NHANES) database (2005 to 2010).

Study IV

Undesired insulin associated weight gain has been a continued challenge in hypoglycemic therapy within Type 2 diabetes. However, if prediction of insulin associated weight gain was possible, screening on an individualized level could be conducted and targeted initiatives could be initiated to avoid or reduce weight gain. The aim of this study was to identify predictors of weight gain in insulin treated patients with Type 2 Diabetes included in the randomized controlled Copenhagen Insulin and Metformin Therapy (CIMT) trial.

STUDY I

Toward Big Data Analytics: Review of Predictive Models in Management of Diabetes and Its Complications

Cichosz, Simon Lebech; Dencker Johansen, Mette; Hejlesen, Ole K
Diabetes Science and technology, 2016

INTRODUCTION

With the arrival of electronic medical records, more information on physician-patient interactions is being captured and stored electronically. This era of 'big health care data' provides rich opportunities for pooling data and for exploring aspects of health care management and for predicting therapeutic outcomes that would otherwise defy analysis. Combining numerous information from several healthcare providers about the patient would increase the level of information significantly.

Predictive models using various methods - from statistics to more complex pattern recognition - have the potential to fuse different kinds of patient information and output prognostic results in a clinical setting[40]. This could be used for clinical decision support, disease surveillance and population health management to improve patient care [8].

Diabetes is one of the top priorities in medical science and health care management; and an abundance of data and information on these patients is therefore available. Diabetes is a very serious disease that can lead to a large number of very serious long-term complications such as blindness, amputation and heart disease if not treated properly in time [2–4]. Also, early stages of Type 2 diabetes are asymptomatic, so patients may go undiagnosed for years [41]. Treatment, especially with insulin, is not without adverse effects such as risk of hypoglycaemia and weight gain [1 42]. Predictive models could potentially inform the management of these diabetes-related problems. Fortunately, the past few decades have seen rapidly growing awareness of the possibilities in the field of using available information for predicting diabetes outcomes. The amount of published papers has risen every year from five publications in 1990 to about 300 in 2015 [43] as illustrated in Figure 5.

The aim of the present paper is to narratively review the literature on predictive models in screening for and the management of prevalent short- and long-term complications in diabetes. This could help facilitate the importance of this scientific area and focus future research on what have been done and what should be the next step.

PREDICTIVE MODELS

Predictive models often include multiple predictors (covariates) to estimate the probability or risk of a certain outcome or to classify *that* a certain outcome is present/absent (diagnostic prediction model) or *will happen* within a specific timeframe (prognostic prediction model) in an individual [44].

Almost any statistical regression model can be used as a predictive model. Generally, there are two kinds of models: parametric and non-parametric ones. Parametric models make assumptions regarding the underlying data distribution, whereas non-parametric models (and semi-parametric models) make fewer or no assumptions about the underlying distribution. The most common approach is to use a regression

model for prediction. This often also involves the use of classic statistical methods to construct the mode based on level of statistical significance [27]. Other, less common model approaches resort to complex mathematical analytics of the data. These models often utilize a broad range of methods involving machine learning and pattern recognition, among others, [38,45], and they are often, but not always, limited to classification tree, neural network, k-nearest neighbor [38].

The model is often trained on large number of individuals of the cohort and validated on a faction of the cohort data or on data from another study. Data could typically consist of single measurements or a time-series. In either case, some kind of signal processing or mathematical transformation is needed to extract relevant predictors.

Whether simple parametric methods like linear regression or more sophisticated methods are deployed, c-statistics (ROC curve) and sensitivity/specificity are often used to evaluate the performance of the prediction model. Furthermore, each approach has pros and cons; however, an in-depth discussion of these aspects falls outside the scope of the present review.

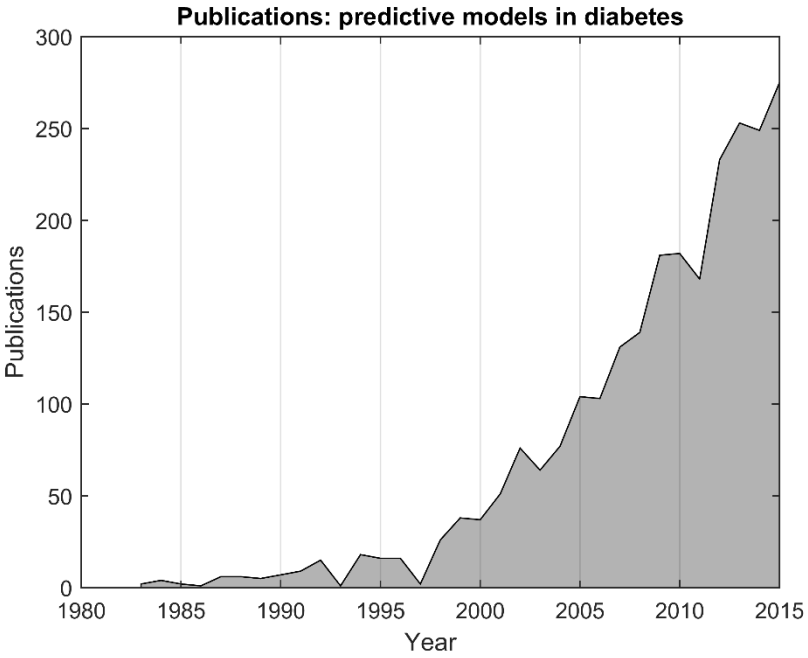

Figure 5 - Number of publications index by PubMed with keywords "predictive AND model AND diabetes." The 2015 count is extrapolated based on the number from May 27, 2015.

PREDICTION MODELS FOR SCREENING

In the United States alone, an estimated 7 million people have undiagnosed diabetes [46]; and when they are finally diagnosed, up to 30% show clinical manifestations of complications of diabetes. Early diagnosis of patients with Type 2 diabetes is thus very important, not least because intensive diabetes management can considerably reduce long-term complications [5–7].

Screening entire populations is not cost-effective, and screening should therefore be restricted to groups that are at high risk for diabetes [25,26]. Models predicting who are at risk for diabetes (prevalence) [47–56] or for developing diabetes in the near future (incidence)[51,57–69] have therefore attracted much interest in the medical literature. Most models are variants of multivariable linear regression models; and most use

anthropometric, anamnestic and demographic information as predictors. The most common predictors included in these models are: body mass index (BMI), age and family history of diabetes and hypertension [27]. However, although the number of prediction models developed is large, only very few end up being used in clinical practice. The reasons for this are legion and mainly involve methodological shortcomings and a generally insufficient level of reporting in the studies in which the screening prediction models were developed. More specifically, the problematic issues typically encompass which predictors were included, how continuous variables were dichotomised, how missing values were dealt with, how adequate statistical measures were reported, or which procedures were used for validating the results [27]. Furthermore, poor design and reporting could entail skepticism regarding the reliability and the clinical usefulness of a model. Debatably, regardless of how the model is developed, all that in the end matters is that the model works in a clinical setting. A typical problem in this respect is that when a model is externally validated in another sample, its accuracy often declines. This is, for example, the case with the model by Bang et al. [48] where the sensitivity/specificity dropped from 79/67% to 72/62% in the external validation. Moreover, temporal validation also showed a drop (63/72%) in this model [54].

PREDICTION MODELS FOR LONG-TERM COMPLICATIONS

RETINOPATHY

Diabetic retinopathy is a primary cause of blindness worldwide [32], and this serious complication of diabetes is already present at the time of clinical diagnosis of Type 2 diabetes in some patients [70]. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 3.6% of patients with type 1 diabetes and 1.6% of patients with Type 2 diabetes were blind [71]. It is recommended that patients with Type 2 diabetes should have an initial comprehensive eye examination by an ophthalmologist or optometrist shortly after being diagnosed with diabetes [2]. Subsequently, the patient should be included in a screening program [72]. The optimal interval for screening of this group of patients with diabetes is not certain; yet, in Denmark, patients are typically seen

once a year depending on the progression of the disease [73]. There is a long latent period before visual loss, and progression of this disease is to large extent preventable and treatable.

Several studies have focused on individualising the screening interval based on risk factors for retinopathy progression [74–76]. Looker et al. [76] used hidden Markov models to calculate the probabilities of extending the interval for people with no visible retinopathy. The results showed that extending the interval involved only a small risk. Mehlsen et al. [77] constructed a multiple logistic regression model to adjust the screening interval in low-risk patients. The model on average prolonged the screening interval 2.9 times for type 1 diabetes patients and 1.2 times for Type 2 diabetes patients. Predictors included in the model were HbA1c, number of retinal haemorrhages and exudates, longer diabetes duration and blood pressure. Others have published a model usable for selecting a high-risk group among newly diagnosed patients with diabetes. This model was suitable for remote areas of the world and for developing countries with limited resources [78]. Convincing evidence for using predictive models for treatment and prevention of retinopathy are yet to be seen. Retinopathy is a feared complication among patients and, in general, the costs of offering frequent screening to all patients are small.

NEUROPATHY

Diabetic peripheral neuropathy is frequent, and 50% of people with Type 2 diabetes have neuropathy and therefore feet at risk of developing diabetic foot ulcer [79]. Diabetic neuropathy is known by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes." Food ulcer is one of the major complications in patients with diabetes, with a 15% lifetime risk of amputation. The risk of having a lower extremity amputation is up to 40 times higher among patients with diabetic than among the background population without diabetes [80].

It has been reported that with early detection and proper multi-disciplinary treatment, the amputation rate can be reduced by up to 60-85% [79,81].

Many potential risk factors have been investigated over the years [82]. However, much less attention had been devoted to developing and validating multivariate prediction models [83–86]. In 2006, Boyko et al. [83] followed 1,285 diabetic veterans and published a prediction model based on seven commonly available clinical variables for development of foot ulcers. Later Monteiro-Soares & M. Dinis-Ribeiro [86] validated and updated Boyko et al.'s model in different settings. Monteiro-Soares & M. Dinis-Ribeiro included information about patients' footwear and increased the prediction capabilities from a receiver-operating characteristic (ROC) area under the curve (AUC) of 0.83 to 0.88. Yet, no fixed system has eventually been adopted, and the implementation of validation models in clinical practice remains limited [84]. The potential of foot ulcer prediction models is large, but more studies are needed.

HEART DISEASE

Diabetes is a well-known risk factor for coronary heart disease. Diabetes adds an about two-fold risk for a wide range of vascular diseases, independently of other conventional risk factors [87].

Much research has been conducted in the field of developing predictive models or risk scores for at-risk individuals from the general population [88]. One of the best models is the Framingham score [89], which has been widely accepted and includes diabetes as a predictor. Several scores have been developed specifically to predict heart disease in patients with diabetes [89–101]. The AUC of these models ranges from 0.59 to 0.80. Typically, a Cox regression model or a logistic regression is used for prediction. The most frequently included predictors are sex, age, systolic blood pressure, cholesterol and smoking. Despite much effort within this field, most models still need to be proven valuable in daily care. According to the International Diabetes Federation, these models fall short of adequacy / are limited because they have not been proven useful in populations older than 65 years and because they have been applied in people in whom treatment to prevent heart disease had already been initiated[72]. Future research should focus on the impact of using coronary heart disease prediction models in the daily care of diabetes patients [88].

PREDICTION MODELS FOR SHORT-TERM COMPLICATIONS

HYPOGLYCAEMIA

People with type 1 diabetes often experience episodes of hypoglycaemia because they need to reduce the level of blood sugar by using insulin [42]. Also patients with Type 2 diabetes may experience episodes of hypoglycaemia because of the increasing use of insulin in this group. The fear induced by hypoglycaemia is pronounced, and the clinical results of this condition are serious. The literature suggests that the incidence of hypoglycaemia requiring emergency assistance reaches 7.1% per year among patients with diabetes [102] and that as many as 6% of all deaths in patients with type 1 diabetes are due to hypoglycaemia [103–105].

The arrival of the Continuous Glucose Monitoring (CGM) system made it possible to frequently measure interstitial blood glucose, and many scientists have since investigated the opportunities offered by this new technology. However, using the CGM for prediction of hypoglycaemia involves accepting a certain proportion of false positive alarms [106–109]. Hypoglycaemia affects the entire autonomic nervous system, including the heart, the brain and perspiration [110,111]. This has led to development of prediction systems that include information from EEG, skin impedance measurements and electrocardiograms [107,112–114]. Some have attempted to use the glucose content in perspiration to predict blood glucose levels [115,116]. Moreover, the use of signal processing to make the CGM signal more accurate has also been investigated [117]. Many methodologies have been explored in pursuit of finding the Holy Grail in reducing hypoglycaemia using a predictive alarm system. However, the differences in styles of reporting and uses of data essentially make these systems incomparable.

One of the main challenges in predicting or detecting an early onset of a hypoglycaemic event is the lack of high-quality data for validating predictive models. It is known that CGM has a physiological lag time and, moreover, less precision in the lower glucose concentration range [118–120]. Knowing the underlying blood glucose level is therefore necessary. One way to obtain such knowledge could be by

establishing access to a large, open database, as seen in other fields such as the MIT-BIH Arrhythmia Database [121]. This would make validation and comparison between the proposed models much more transparent and easy.

INSULIN-ASSOCIATED WEIGHT GAIN

In most patients with Type 2 diabetes, it will eventually be necessary to begin insulin treatment to achieve the therapeutic goal of HbA_{1c} < 7 mmol/l (126 mg/dl) [1]. The problem of weight gain induced by insulin has long been documented as an issue in diabetes treatment [30,122]. In the Diabetes Control and Complications Trial (DCCT), the average weight gain of patients with type 1 diabetes undergoing intensive treatment was 5.1 kg compared with 2.4 kg in standard treatment arm, [123] and similar results are seen for Type 2 diabetes [124]. This increase in weight can negatively affect the cardiovascular risk profile and increase morbidity and mortality when intensive treatment is postponed due to the patient's fear of gaining weight [30]. Prediction of insulin-associated weight gain has attracted only little attention in the literature [125–127] compared with other complication of diabetes. It is known that insulin dosage is a strong predictor of weight gain [128]. Jansen et al. [125] followed 65 patients with diabetes during insulin treatment, and they proposed a regression model for "prediction" of weight gain. However, the model is not suitable for prospective usage as it requires data on 0-12 months of insulin dosage and any changes in insulin dosage. In addition, common performance measures are not reported in this study. Balkau et al. [126] reported data on factors associated with insulin-associated weight gain in 2,179 patients with Type 2 diabetes. They also proposed a model that could explain part of the weight gain, but their model was not operational for prospective usage in the clinic. Factors included in this model were HbA_{1c} , BMI at baseline and information about insulin. In future, more studies within this new field are needed.

DISCUSSION

Predictive models drawing on and analysing 'big data' are being used for the handling of many daily-task applications. Much sparser use has been made of predictive models in clinical practice, however [72,129]. There are many reasons why this is so. First, a prediction model must provide valid and accurate estimates, and these estimates should be able to inform management and clinical decision-making and subsequently improve outcome and cost-effectiveness of care. Second, a prediction model must be accepted and understood by clinicians in order for the model to be adopted on a wider scale. These requirements often imply that the models become oversimplified, which could weaken their accuracy. Convincing documentation and evidence for all relevant aspects must be provided, which is not always possible in a pragmatic context. Prediction models are therefore often based simply on multiple logistics or similar linear regression. The advantage of this approach lies in the transparency of its functionality; however, this advantage comes at the cost of not taking into account that predictors are rarely independent. In future work, it would be interesting to further explore the potential of other methods taking predictor dependencies into account. Ultimately, prediction models have to prove useful in terms of impact, i.e. better patient outcome [44,130]. Such studies are time-consuming and expensive, and these impediments will have to be fought to reap the full benefit of the 'big clinical data' available.

Much effort have been put into developing predictive models for use in the management of diabetes and its complications. However, in general, most of these models have not been implemented and the clinical impact has not been investigated. Although evidence from implementation is lacking, it is argued that predictive models do have the potential to transform the way healthcare providers use sophisticated technologies; and much insight may be gained and more informed decisions made by drawing on the large amount of electronically stored clinical data.

STUDY II

Improved Diabetes Screening Using an Extended Predictive Feature Search

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Diabetes Technology and Therapeutics, 2014

Mary Ann Liebert, Inc. publishers

INTRODUCTION

The prevalence of Type 2 diabetes is increasing, and the disease is associated with a major increase in morbidity, mortality, and healthcare costs [10]. In 2010, the prevalence of Type 2 diabetes in the United Kingdom, United States, China and Arabic Emirates ranged from 7% to as high as 34% of the population [12,13]. In the US, an estimated 7 million people have undiagnosed diabetes [46], and when finally diagnosed, up to 30% show clinical manifestations of diabetic complications [14]. Early diagnosis of Type 2 diabetes is thus very important, as intensive diabetes control can significantly reduce long-term complications [5–7].

In as much as screening entire populations is not cost-effective, priority in the screening process must rely on selecting those people at high risk for diabetes [25,26]. Several studies of diabetes screening have been published during the last decade [12,27].

Risk prediction or risk stratification models have a substantial potential to be utilized in a screening context in order to identify high risk individuals who would subsequently undergo testing for diabetes. These models often include a combination of predictors, such as anthropometrics, lifestyle, hereditary conditions and clinical measurements [27]. Multivariable statistical methods, i.e. logistic regression, are used to combine these risk predictors into a model [27,131]. Despite the large number of proposed models, not many are used in daily clinical practice. Optimal model performance is crucial for all tests. Most models are based on elimination of predictors with focus on statistical significance of the model which may not yield optimal performance [27]. Cohort data obtained for a different scientific purpose is often used, and this can limit the models' use in an entire population. Furthermore, attempts are often made to construct models that present risk scores that reflect the complexity of the data, but which also may be perceived as simple and applicable in clinical practice. This is commonly done by collapsing continuous variables into two or more categories, or preselecting predictors based on subjective judgment [132]. From a performance point of view, this may lead to an oversimplification and deterioration of the effectiveness of the proposed models [133,134].

In the present study, we investigated the feasibility and performance of a model based on extended predictive features and compared it with to two widely accepted models.

RESEARCH DESIGN AND METHODS

We used data from multiple years of the National Health and Nutrition Examination Survey (NHANES , 2005 to 2010) [135], where results from an oral glucose tolerance test (OGTT) and a fasting plasma glucose (FPG) test were available to identify persons with undiagnosed diabetes using a logistic classification model.

The NHANES is a cross-sectional study conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. To represent the U.S. population, NHANES used complex, multistage probability sampling of the civilian, non-institutionalized population. To produce reliable statistics, NHANES oversampled elderly persons and some racial and ethnic minorities. The participants

were limited to those aged 20 and above. Pregnant women and participants with diagnosed diabetes were excluded. Based on these data, we developed and tested a new model for diabetes screening and compared it with two accepted screening models.

Selection of predictors to be included in this new model as well as validation of the model was done by v-fold cross-validation. We calculated all 16,383 possible combinations of predictors in order to find the optimal subset. We derived and tested the model on all combinations of 9 (of 10) partitions of training data and 1 (of 10) partitions of test data. The accepted statistical methods ensured valid testing of the model performance, reducing generalization bias [45,136].

END POINT

Our primary objective was detection of undiagnosed diabetes (prevalence) in the cohort of NHANES. OGTT results above or equal to 11.1 mmol/l or FPG above 7 mmol/l were used as thresholds for the diagnosis of diabetes. ADA recommends that a test result diagnostic of diabetes should be repeated to rule out laboratory error, unless the diagnosis is clear on clinical grounds [137]. Multiple test results were not available in our dataset, so one positive test was considered to be a diagnostic criterion.

PREDICTIVE VARIABLES

Multiple variables were selected to be investigated for their ability to distinguish between non-diabetics and undiagnosed diabetes. We selected a number of well-established risk factors, such as age, BMI and hereditary conditions [138–141], all available in the NHANES data set. In addition, we selected a number of more uncertain predictors, such as self-perceived oral health [142], which can be an early complication of diabetes [143] and socioeconomic status in the form of income and educational level, which have been associated with diabetes-related mortality [144].

Possible predictor candidates were age, sex, family history of diabetes (yes/no) (questionnaire), history of hypertension (yes/no?) (questionnaire), BMI (body mass index), physically activity (yes/no) (questionnaire), waist circumference, educational level (questionnaire), income (questionnaire), race, self-perceived health (questionnaire), nicotine use (questionnaire), self-perceived dental condition (questionnaire) and blood pressure .

The NHANES questionnaire concerning physical activity was changed from 2006 to 2007 and forward. We considered the participants to be physically active if they answered "yes" to the question: "Over the past 30 days, did you do any vigorous activities for at least 10 minutes that caused heavy sweating, or large increases in breathing or heart rate?" in the 2005-2006 cohort, or the question: "Do you carry out any vigorous-intensity sports, fitness, or recreational activities that cause large increases in breathing or heart rate, like jogging or basketball, for at least 10 minutes continuously?" in the 2007-2010 cohort. Participants' family histories of diabetes were considered as binary without considering which family member had diabetes. Assessment of self-perceived oral health was formulated as "Rate the health of your teeth and gums" on a scale from 1(excellent) to 5 (poor).

MISSING DATA

We used multiple imputation to replace missing values. This imputation technique involves creating multiple copies of the data and replacing missing values with imputed values on the basis of a suitable random sample from their predicted distribution. Table 2 gives the distribution of missing values between variables included in the modeling. Multiple imputations allow patients with incomplete data to be included in analyses, thereby making full use of all available data and increasing precision and power without compromising validity [145].

COMPARISON WITH CONVENTIONAL MODELS

Bang et al. (2009)[146] used data from NHANES 1999 to 2004 to model and develop a "patient self-assessment score" for use in a wide variety of community settings and clinical encounters (including patient waiting rooms or on the Internet) via a simple pencil-and-paper method. In brief, the model was compared to several other scoring systems and validated on a cohort of approximately 21,000 participants, the primary end point being diagnosis of diabetes. The final model included variables of age, sex, obesity (BMI), history of hypertension, family history of diabetes and physical activity predictors, and was simplified for user-friendliness and presentation. Not many proposed models have been designed for and validated on an entire adult population (age > 20). This is one advantage of using the model formulated by Bang et al. (2009) as a foundation for comparison with our new model. In addition, we also used a model by Baan et al. (1999) [147], developed from a European Dutch population, for comparison. In brief, participants from the Rotter dam Study aged 55–75 years, not known to have diabetes completed a questionnaire on diabetes-related symptoms and risk factors and underwent a clinical examination. The main findings from Baan et al. (1999) were that the additional information from the questionnaire sparsely improved the prediction capability compared to using routinely collected data only.
We evaluated prediction models through sensitivity and specificity for pre-determined cutoff points and receiver operating characteristics (ROCs) based on logistic regression models comparing the area under the curve (AUC) of the new model with that of the sparser models proposed by Bang et al. (2009)[146] and Baan et al. (1999). We used student's t-tests or z-tests for proportions in order to compare the difference between the groups with and without diabetes.

RESULTS

A total of 51 participants with diagnosed diabetes and 203 pregnant women were excluded. Thus, the study included a total of 5398 participants. The cohort characteristics are given in table 2. This cohort included 478 (8.8%, 478 of 5398)

patients with undiagnosed Type 2 diabetes. Participants with undiagnosed diabetes had a tendency to be older, had a lower level of physical activity level, higher waist circumference and BMI, were less educated, earned less income, had less use of nicotine and higher incidence of diabetes in their families than their counterparts without diabetes ($P<0.05$).

The final model, selected on the basis of performance from all possible combinations of predictors, was composed of BMI, waist circumference, age, history of hypertension, family history of diabetes, physical activity, education level and race. Figure 6 presents the ROCs for the two models. The established models had AUCs of 0.74 and 0.71, respectively, compared with an AUC of 0.78 ($P<0.05$ for both comparisons) for the new model. Table 3 presents sensitivity, specificity, positive predictive value and negative predictive value at proposed cutoff points by Bang et al. (2009) compared to the new model and the model by Baan et al. with fixed specificity. For the cutoff point of 4 (risk score), the established models yielded sensitivities of 82% and 57%, respectively, 95% CI [79.4; 83.7 %] and [55.1; 58.5 %] and a specificity of 56% for both. The new extended model yielded a sensitivity of 85% with 95% CI [83.1; 87.6 %] when the specificity was maintained at the same level.

Table 2 - Table presents the characteristics for the population studied, data presented as mean ± standard deviation (sd) or proportion of the group. Missing data describe the percentage of participants lacking information about a particular predictor. NS = not Significant.

Variable name	Missing N(%)	Non-diabetics N=4920	Diabetics N=478	P value
BMI (kg/m²)	8.5%	28 ±6.4	31 ±6.6	*P<.05*
Waist (cm)	1.8%	97 ±15	106 ±15	*P<.05*
Gender (women %)	0	2465 (50%)	215(45%)	*P<.05*
Age (years)	4.8%	47 ±16	60 ±14	*P<.05*
History of family diabetes? (yes %)	0	1824(37%)	201 (42%)	*P<.05*
Physically active? (yes %)	0	1331 (27%)	43 (9%)	*P<.05*
Told high blood pressure (yes %)	0	1429(29%)	25 (53%)	*P<.05*
Told high cholesterol (yes %)	30%	2070 (42%)	220 (46%)	NS
Education level (%)	0	-	-	-
- Less than 9th grade	-	490 (10%)	86 (18%)	*P<.05*
- 9-11th grade	-	736 (15%)	82 (17%)	NS
- High school grad or equivalent	-	1183(24%)	143 (30%)	*P<.05*

- Some college or AA degree	-	1380(28%)	105(22 %)	*P<.05*
- College graduate or above	-	1134(23%)	62 (13%)	*P<.05*
Ratio of family income to poverty	7.2**%**	2.63 ±1.6	2.47 ±1.5	*P<.05*
Race / Ethnicity (%)	0	-	-	-
- Mexican American	-	884 (18%)	96 (20%)	NS
- Other Hispanic	-	441 (9%)	43 (9%)	NS
- Non-Hispanic White	-	2465 (50%)	268 (56%)	*P<.05*
- Non-Hispanic Black	-	887 (18%)	268 (12%)	*P<.05*
- Other Race (Including Multi-racial)	-	243 (5%)	14 (3%)	NS
Self-perceived health (1-10)	3.7**%**	2.72 ±0.9	2.97 ±1.0	NS
Nicotine use (yes %)	3.9**%**	1282 (26%)	105 (22%)	*P<.05*
Self-perceived dental cond. (1-10)	8.1**%**	3.23 ± 4	3.65 ± 7	NS

For the cutoff point of 5 (risk score), the established model yielded sensitivity of 63% and 42%, respectively, 95% CI [61.7; 65.1 %] and [40.7; 42.9] and a specificity of 72%. The new model yielded a sensitivity of 70% (95% CI [68.2; 71.9 %]) when the specificity was held at the same level. The new model thus yields better sensitivity at both cutoff points. The increased sensitivity from the new model corresponds to discovering 33 additional patients with diabetes compared to Bang et al. (2009) and an additional 129 patients compared to Baan et al. when the cutoff point of 5 (risk score) is used in the population sample.

The total computation time for all predictor combinations for the new model took approximately 8 hours on a standard laptop (Dell, Intel Core i5-2410 CPU @ 2.30 GHz, 4 GB ram, 64-bit) using a self-written algorithm (MATLAB® R2011b, Mathworks, Massachusetts, U.S.A).

Tabel 3 - Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different cutoff points. Sensitivities are shown with 95% confidence interval.

Table 2 NHANES 2005-2010 (N=5398)	**Models**	**Sen.%**	**Spe. %**	**PPV %**	**NPV %**
Cut-off > 4	New model	85 [83.1;87.6]	56	14	98
	Bang et al. ≥ 4	82 [79.4;83.7]	56	13	97
	Rotterdam	57 [55.1; 58.5]	56	9	94
Cut-off > 5	New model	70 [68.2;71.9]	72	18	97
	Bang et al.≥ 5	63 [61.7;65.1]	72	16	96
	Rotterdam	42 [40.7;42.9]	72	11	94

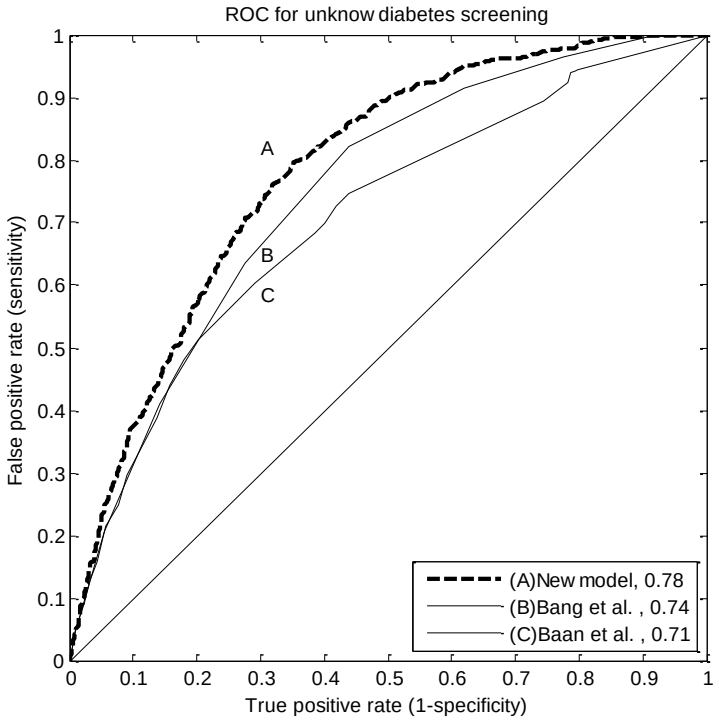

Figure 6 - ROC curve for the detection of undiagnosed Type 2 diabetes. (A) = Logistic model including age, sex, family history of diabetes, history of hypertension, BMI, degree of physical activity, waist circumference, education level, income, race, health, nicotine use, dental condition, blood pressure. (B)= Bang et al. screening score (1-10) (based on age, sex, family history of diabetes, history of hypertension, BMI, physically activity). (C) = Baan et al. screening score, using age, anti-hypertension medication, BMI and gender as predictors; uses the oral glucose tolerance test or fasting plasma glucose as the reference standard.

DISCUSSION

Numerous diabetes prediction models have been developed over the years [12,27,131,132,146–149], and most studies use modeling approaches focusing on simplicity and statistical selection of predictors rather than performance. Most studies also use specific cohorts, which often exhibit small age ranges or racial/ ethnic origin groups, thus limiting their generalizability to an entire population. We explored whether an

extended investigation of predictor combinations could lead to better performance in a diabetes screening model for a population of people over age 20.

Our results show that information about education level, racial/ethnic origin and waist circumference can significantly improve sensitivity and specificity of an established model when screening for diabetes by using a full investigation of possible predictor combinations. Using this kind of information can help reduce unwarranted screening for Type 2 diabetes, thus lowering costs[26] of performing additional test such as HbA_{1c}/OGTT for high-risk persons. Waist circumference and/or BMI have been used in most models [131,132,146–149], as has racial/ethnic origin, which is not surprising, as we know that racial differences are associated with the development of diabetes in some groups [53]. To our knowledge, information about education level has not been used in screenings models, possibly because this kind of data is related to diabetes through lifestyle. Overall, however, it seems sensible to include this information. Saydah et al. have shown that having less than a high school education was related to a 2-fold higher mortality from diabetes, after controlling for gender, age, ethnicity, marital status, and BMI [144].

The performance of the established model by Bang et al. (2009)[146] in the present cohort was different from that originally reported when we examined it on our cohort. The cutoff point was ≥ 4 (risk score) and sensitivity and specificity were reported between 91-97 % and 38-51 %. Our validation yielded sensitivity and specificity levels of 82% and 56%, respectively. The major difference between the studies was that we used a diagnostic criteria based upon FPG and OGTT, whereas the Bang model used only FPG, possibly because OGTT was only available in one of the two validation datasets. From the perspective of the ROC, the model by Baan et al. (1999) [147] performed equal to that of Bang et al. (2009) for specificities above 80%. Below this threshold, however, the performance of Baan et al.'s model is inferior. Baan et al.'s model was originally developed and validated in a cohort aged 55 and above, which might explain the poor performance of the algorithm on a cohort which used an entire adult population.

These findings highlight the difficulties of comparing results across different population samples, even when identical underlying sample techniques are used. Models generally perform best on the data for which they have been developed, and they perform better on a training dataset than on a validation dataset [136]. We used the accepted cross-validation approach, which is basically an average of the performance of multiple models [45,136]. Our main concern when using this approach is the representativeness of the participants included in the study. NHANES uses complex, multistage probability sampling of the civilian, non-institutionalized population to create a realistic and representative sample of the U.S. population. Participants included in this study had an undiagnosed diabetes prevalence of 8.8%, which is significantly higher than the estimates from the International Diabetes Federation (IDF), which cite 2.6-3.4% of the U.S. population [150]. Although our cohort is believed to be representative of the U.S. population, it should be emphasized that elderly persons and some racial and ethnic minorities, with higher prevalence of diabetes, have been oversampled in the NHANES. However, the comparison of our new model with the established models tested under similar conditions is valid, without a potential bias from the sampling. Several other studies have used (earlier) versions of the NHANES for the purpose of developing a diabetes screening model [53,146].
Our end-point was undiagnosed diabetes by definition, although incidence prediction of diabetes and people with impaired glucose tolerance, also known as prediabetes, was beyond the scope of this study. In many respects, however, these issues are similar to those we have investigated. Hence, we believe our approach could add to these models as well [21]. For a model to have generalizability over time and to other populations, the model needs to be validated precisely with respect to these factors [136]. Further validation of our screening approach with other samples and for other uses is therefore important.

When developing models to predict undiagnosed diabetes, it is necessary to maintain a balance between including too many model variables and too few[151]. Automated variable selection methods have been used in most studies involving prediction of diabetes. Collins et al., in a systematic review of diabetes prediction, showed that

56% of the studies used automated variable selection to develop their model [27]. These methods are suitable for pre-specified hypothesis testing, but in a predictive/classification approach, where performance is the goal, these techniques may not always yield optimal performance and in some cases may also create unstable models [152].

The artificial simplicity presented in most models developed over the last decade is based on the belief that simplicity is the key in implementing a model successfully and in ensuring that it is accepted widely. Nevertheless, almost all models could easily be implemented in a standard webpage and made available for clinical use or to the public and still maintain the complexity without oversimplification. Our findings, based on a relatively large dataset of 5398 participants encompassing fourteen variables, showed that it is feasible to do a full investigation of the optimal subset of predictors to be included in the model. It should be noted, however, that in more complex datasets focusing on classification, elimination methods from machine learning can be used with success in a medical context [153]. In brief, machine learning concerns the development and study of systems that can learn from data.

We have shown how simple healthcare and economic data (such as ratio of family income to poverty) can help determine who is most at risk for undiagnosed diabetes. We have also shown that a calculation of all possible predictor combinations is feasible and can improve the performance of the predictive model.

STUDY III

A Novel Model Enhances HbA1c-based Diabetes Screening Using Simple Anthropometric, Anamnestic, and Demographic Information

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Journal of Diabetes, 2014

Journal of Diabetes

INTRODUCTION

Diabetes and its complications are major causes of morbidity and mortality worldwide. An estimated 25.8 million U.S. citizens (8.3%) have diagnosed or undiagnosed diabetes[46]. The early stages of diabetes are asymptomatic, so people may go undiagnosed for years [41]. Approximately 7 million people or one third of the entire population with diabetes in the U.S. have undiagnosed diabetes [46]. Early diagnosis is important as early initiation of careful diabetes management can reduce long-term complications [5,6]. Screening for diabetes can therefore be helpful in preventing major health problems in a large portion of the population.

There is no clear consensus on the optimal screening test for detection of unknown diabetes. The most widely used tests include the oral glucose tolerance test (OGTT)

and the fasting plasma glucose (FPG) test [18]. The OGTT test is considered the "golden standard" for detection of diabetes because it reflects some of the pathophysiological responses seen in diabetes. However, both the OGTT and the FPG require the patients to be fasting for at least 8 hours, and OGTT is time-consuming, expensive, and inconvenient for the patient. Furthermore, repetition of the FPG if initial results are positive is required to confirm the diagnosis, and the test is not as reliable as expected [154,155]. The glycated hemoglobin (HbA_{1c}) test has been suggested as an alternative screening test for Type 2 diabetes and it has also been added as a first choice diagnostic criterion [137,156]. Despite many advantages of using the HbA_{1c} test, its sensitivity for finding latent diabetes, such as for screening purposes, compared with that of the OGTT may not be as sensitive[19–23] - this is not unexpected as protein hyperglycation occurs secondary to abnormally high blood glucose, but there are limited data on how long the delay is. [157]. Also intersubject variability in the form of biological factors may contributor to the level of glycation in different individuals [158]. We previously showed in newly diagnosed Type 2 diabetes patients that postprandial abnormalities were more pronounced than elevated HbA_{1c} [159].

Colagiuri and colleagues showed in a large data-pooling analysis that association of FPG, OGTT, HbA_{1c} and retinopathy was similar between measures in relative numbers [160]. In absolute quantities OGTT screening diagnoses more patients also containing most patients from HbA_{1c} and FPG screening [21]. Epidemiological studies have shown that a diabetes HbA_{1c} threshold of 6.5% (48 mmol/mol) identifies only between 30 and 40% of previously undiagnosed patients with diabetes, whereas an OGTT identifies approximately 90% [21,157]. The American Diabetes Association (ADA) similarly state this HbA_{1c} sensitivity problem in their 2013 position statement of diagnosis and classification of diabetes mellitus and recommend more research in the area [161].

ADA also states that screening for diabetes should always be done in the pragmatic context of the patient's life condition [137]. In practice, the patient's health information is taken into account, but to our knowledge, no screening method compares the use of this information within the context of a complete model for screening adults with

HbA_{1c}. It could be speculated that this information would add value to the accuracy of HbA_{1c} screening [162].

This paper presents a novel screening algorithm for undiagnosed diabetes in multiethnic U.S. adults by using readily available health information combined with HbA_{1c} measurement. Our aim was to improve methods for diabetes screening by using data from the National Health and Nutrition Examination Survey (NHANES) database (2005 to 2010).

RESEARCH DESIGN AND METHODS

STUDY DESIGN AND PARTICIPANTS

We used a logistic regression classification model to combine information of HbA_{1c} and health information for screening of undiagnosed diabetes and compared this approach with screening using HbA_{1c} information alone.

We used data from multiple years of NHANES (2005 to 2010) [135] for which HbA_{1c} and OGTT data were publicly available.
We included participants aged above 20 for whom both HbA_{1c} and OGTT data were available. Pregnant women and participants with known diabetes were excluded. For model fitting, we used multiple logistic regression classification with cases of undiagnosed diabetes as the end point. Undiagnosed diabetes was defined based on a two-hour blood glucose level above 11.1 mmol/L during an OGTT. For each participant, we retrieved data that were collected through physical examinations, interviews, and laboratory tests.

MODEL DERIVATION AND DEVELOPMENT

A model (HbA_{1c} +) based on HbA_{1c} results combined with additional available health information already know to be linked with the development of diabetes [138–141,163] was developed. The additional data were age, waist circumference, body mass index (BMI), gender, a family history of diabetes, and self-assessed level of physical

activity.

We selected additional information data that were reasonably consistent from year to year and where only few data were missing (< 10%). The inclusion criteria for including predictors were mainly based on availability of data form year to year combined with scientific evidence of link between predictor and diabetes.

The NHANES questionnaire concerning physical activity was changed from 2006 to 2007 and forward. We consider the participants to have been physical active if they answered "yes" to the question "Over the past 30 days, did you do any vigorous activities for at least 10 minutes that caused heavy sweating, or large increases in breathing or heart rate" in the 2005-2006 cohort, or if they answered "yes" the question "Do you do any vigorous-intensity sports, fitness, or recreational activities that cause large increases in breathing or heart rate like running or basketball for at least 10 minutes continuously?" in the 2007-2010 cohort. Also the participant's history of family diabetes was dichotomized as a "yes/no" question, i.e. it remained unspecified which other family member was having or had had diabetes.

Backwards elimination was used to remove predictors that did not statistically improve the model. The process was iterative: predictors were removed until each predictor had a statistical significance level of $P < 0.05$.

To avoid over-fitting and to remain able to utilize the entire cohort for validation, a cross-validation approach was used for model training and validation by randomly splitting the cohort into halves (two-fold cross-validation). The first half was used for training, while the second half was used for validation; this was then reversed and the results were averaged. To estimate confidence intervals of area under the curve (AUC) of the receiver-operating curve (ROC) cross-validation was used and the differences between AUCs were tested using a two sample student's t-test.

The results of the HbA_{1c}+ model were compared with the results of the HbA1c alone. We calculated standard validation measures such as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the AUC as a discrimination statistic. We compared the models' sensitivities and specificities for

previously proposed HbA_{1c} cutoff points such 6.1% (43 mmol/mol), 5.7% (39 mmol/mol), and the diagnostic point of 6.5% (48 mmol/mol), [20,164]. The corresponding specificity was matched in our model, and the sensitivity could then be compared between the two approaches. Modeling was done using MATLAB® R2011b (Mathworks, Massachusetts, U.S.A).

MISSING DATA

Because of proportions of missing data, we used multiple imputations to replace missing values. We thereby created multiple copies of data and replaced missing values with imputed values on the basis of a random sample from their predicted distribution. Multiple imputations allow patients with incomplete data to be included in analyses and hence full use of all the available data. This, in turn, increased the precision and the power of the study without compromising the validity of the model [145].

RESULTS

A total of 51 participants with known diabetes and 203 pregnant women were excluded. Thus, the study included a total of 5381 participants. The clinical characteristics of the cohort and the distribution of missing values between variables included in the modeling are shown in Table 4. This cohort included 7.5% undiagnosed Type 2 diabetes patients corresponding to 404 participants.

Table 4 - Table presents the characteristics for the population studied, data are presented as mean ± standard deviation (sd) or proportion of the group. Missing data describe the percentage of participants for whom information about a particular predictor was missing.

Variable name	Missing	Patients without diabetes	Patients with diabetes
HbA_{1c} (%)	0	5.4 ± 0.6	6.4 ± 1.4
BMI (kg/m²)	0.9	28.5 ± 6.4	30.6 ± 6.4
Waist (cm)	1.7	97.8 ± 15.2	105 ± 15
Gender (women%)	5	50	49
Age (years)	4.8	47 ± 17	60 ± 14
History of family	0	37	42

Physically active? (yes%)	0	25	9
Systolic blood pressure	6	123 ± 18	134 ± 21
Diastolic blood pressure	6	69 ± 13	68 ± 17

Participants with undiagnosed diabetes tended to be older, to do less physical activity, to have a larger waist circumference, a larger BMI, a higher systolic blood pressure, and a higher incidence of family diabetes than their counterparts without diabetes. Table 4 presents the final regression models derived from the development using two-fold cross-validation. For the HbA_{1c}+ model, HbA_{1c}, age, waist circumference, and physical activity were significant predictors of undiagnosed diabetes. As seen in Table 4, HbA_{1c} is the most important predictor of undiagnosed diabetes. We assessed the diagnostic characteristics of different cutoff thresholds. Table 5 presents the performance of the models using these cutoff points. Figure 7 represents the ROC for the two methods. As seen from the figure, the HbA_{1c} have a saw-toothed appearance, which indicates that area of activity is much smaller for this method.

Tabel 5 - Sensitivity (Sen), specificity (Spe), positive predictive value (PPV), negative predictive value (NPV) for different proposed cutoff points.

Models	**Sen**	**Spe**	**PPV**	**NPV**
Cutoff point 6.5%				
HbA_{1c}	0.28	0.99	0.75	0.94
HbA_{1c} +	0.28	0.99	0.75	0.94
Cutoff point 6.1%				
HbA_{1c}	0.46	0.95	0.43	0.96
HbA_{1c} +	0.52	0.95	0.46	0.96
Cutoff point 5.7%				
HbA_{1c}	0.74	0.74	0.19	0.97
HbA_{1c} +	0.80	0.74	0.20	0.98

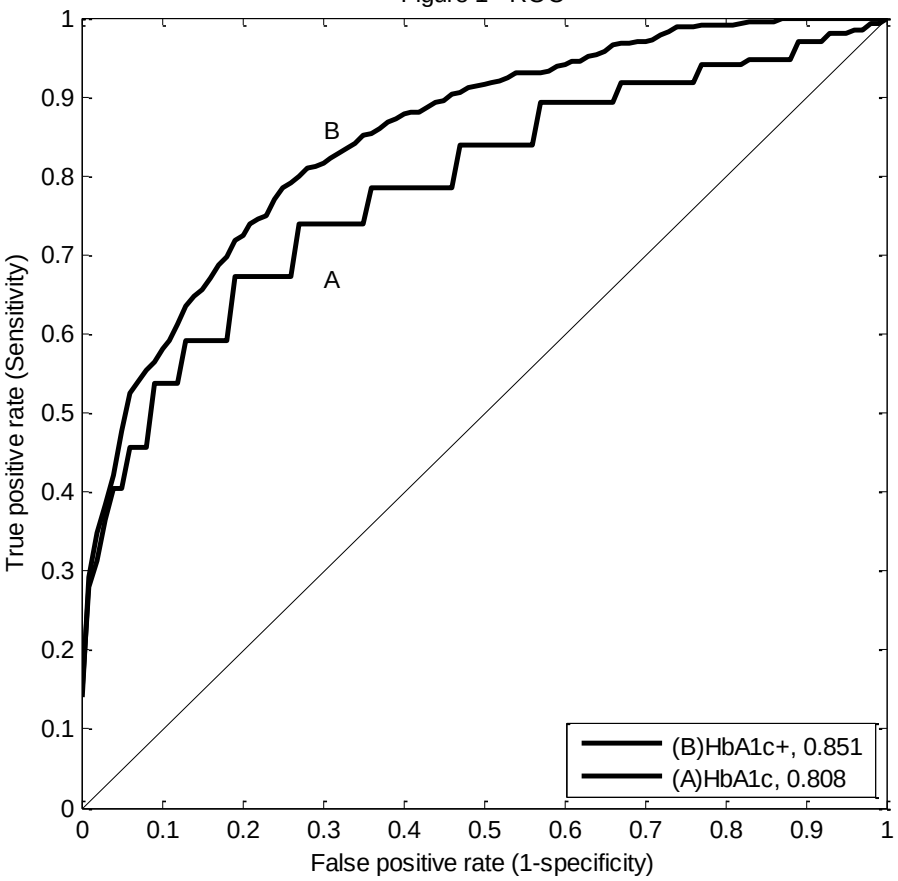
For HbA1c, a cutoff point of ≥ 6.1 (43 mmol/mol) to have a high risk of undiagnosed diabetes; this cutoff point gave a sensitivity of 46%, a specificity of 95%, a PPV of 43%, and a NPV of 96%, with an ROC AUC 0.808 (95% confidence interval (CI 95),

0.786-0.829). For the HbA1c + matching the specificity yielded a sensitivity of 52%, a specificity of 95%, a PPV of 46%, and a NPV of 96% with an ROC AUC of 0.851 (CI 95, 0.827-0.872). For HbA1c, a cutoff point of ≥ 6.5 (48 mmol/mol) to have a high risk of undiagnosed diabetes; this cutoff gave a sensitivity of 28%, a specificity of 99%, a PPV of 75%, and a NPV of 94%; these results were identical for our model. There was a significant difference in the AUC between the HbA1c + model and the model using HbA_{1c} without enhancement ($P<0.05$). The difference was estimated to 0.042 (CI 95, 0.011-0.073).

Figure 7 - ROC curve for the detection of unknown Type 2 diabetes (A) simple cutoff model with HbA1c (B) Logistic regression model including HbA1c, age, waist circumference, and a

question about physical activity - using the oral glucose tolerance test as the reference standard.

Figure 1 - ROC



DISCUSSION

The HbA_{1c} threshold of 6.5% (48 mmol/mol), is recommended to be used to diagnose diabetes, but this threshold gives low accuracy in screening for diabetes.
In the present study, we present a Type 2 diabetes screening model that draws on health care information and blood measurements of HbA_{1c}. The logistic model was associated with an improved sensitivity when HbA_{1c} was used in combination with additional healthcare information, especially for cutoff points with a specificity below <90%. Furthermore, the combined model produced a significantly larger ROC AUC than screening only with HbA_{1c} . These results underline the importance of including covariates with known influence on diabetes diagnostics.

Several studies and reviews have investigated the optimum cutoff point for HbA_{1c}. Most report that the optimum cutoff point is 6.1% (43 mmol/mol). Wiener and Roberts [165] investigated FPG and HbA_{1c} in patients undergoing OGTT. They found results comparable to ours: A HbA_{1c} cutoff point of 6% gave a sensitivity of 51% and a specificity of 98%, while using the FPG with a 6 mmol/l cutoff gave a sensitivity of 90% and a specificity of 66% [165]. In the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, which used comparable cutoff points of ≥ 6.1% (43 mmol/mol), the sensitivities ranged from 78 to 81% and the specificities from 79 to 84% in several studies[166,167]. In our study, this cutoff point offered a poor sensitivity of 46%, but a good specificity of 95%, and the most comparable sensitivity (74%) and specificity (74%) were reached with a lower cut-off value of 5.7% (39 mmol/mol). This difference could possibly be explained by the composition of the population sample. The prevalence of undiagnosed diabetes in the participants in our study was 7.5%, which is significantly higher than ADA estimates, which correspond to nearly 1/3 of 7.5% in the U.S. population. A likely cause of the high prevalence of undiagnosed in the present study is NHANES oversampling of elderly people and racial and ethnic minorities who have a higher prevalence of diabetes than the general population. This problem is not unique for our study, but the problem hampers

accurate comparison across studies. Only few studies recruit from the general population [20], and this fact introduces a potential selection bias . This underscores the need for validating the proposed screening model within the population in which it is intended to be used.

The diagnostic HbA_{1c} threshold for diabetes of 6.5% (48 mmol/mol) yielded a low sensitivity of only 28% for screening purposes, and adding additional information did not improve the sensitivity. This result is in good line with known knowledge regarding screening with HbA_{1c}, where an HbA_{1c} threshold of 6.5% identifies only 30-40% of previously undiagnosed patients with diabetes [157].

We found that, besides HbA_{1c} , measures of obesity (waist circumference), age, and physical activity were important predictors of undiagnosed diabetes in our HbA_{1c}+ model. These findings are in line with previously described diabetes screening models [146,149]. Compared with the results presented by Bang et al. [146], age and obesity were the best predictors of risk. The magnitude of the odds ratios of these predictors was close to what we found.

In a review on HbA_{1c} as a screening tool, Bennett et al. [20] concluded that population-specific cutoff points could be beneficial, as optimum cut-offs vary by ethnic group, age, gender, and the population's prevalence of diabetes. To some extent, our model may be claimed to take account of this fact, but we did not include information about ethnicity/race. HbA1c have several limitations in screening use, the main limitations is the cost of the test which is much higher than FPG and OGTT, also the HbA1c is a poor predictor for impaired glucose tolerance (IGT). Furthermore Herman et al. [168] concluded that HbA1c must be used carefully and in combination with traditional glucose criteria when screening and diagnosing diabetes. In a large dataset with representative samples, this potentially important variable could be included and this would possibly further improve screening.

We used logistic regression as a linear method for modeling. This method is often used in population modeling because population growth follows a logistic curve and has a result that is easy to interpret. But it is possible that methods such as support

vector machine (SVM) or neural network may also improve screening as these methods have been proven to produce good results in applications of machine learning [153]. These methods also include an option for non-linear solutions. Further research should consider these possibilities when developing screening models within this area.

It has been suggested that ROC curves should be used to find the optimal cutoff point in screening tests [169]. The optimal cutoff point for maximizing sensitivity and specificity in ROC curves is defined as the 45 tangent in the upper left corner of the curve. However, this may not be the optimal cutoff point for a clinical test because practical considerations and the seriousness of the disease must also be taken into account when screening. We chose to compare sensitivity between models with a similar specificity derived from suggested cutoff points for HbA_{1c} as screening tools. This makes it possible to compare different methods pairwise, but in practical use, the optimal sensitivity and specificity may, indeed, be very different. If high specificity is preferred, the additional gain from using our models is sparse. The AUC presented is based on calculations with trapezoidal approximation between discrete steps in the empirical ROC to estimate the area. This leads to an overestimation of the AUC for screening with only HbA_{1c}. The (A) AUC in Figure 7 for HbA_{1c} is significantly lower if more discrete steps are added equivalent to the number of steps in (B) HbA_{1c}+. The HbA_{1c} AUC is then estimated to 0.787 (CI 95, 0.766-0.807) instead of 0.808. In future studies we also need to investigate ways to implement and to present the model as a tool in a clinical setting.

In conclusion, we developed a simple screening model which could help improve screening for patients with undiagnosed Type 2 diabetes with HbA_{1c} by adding additional healthcare information.

STUDY IV

Prediction of Excessive Weight Gain In Insulin Treated Patients with Type 2 Diabetes

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Journal of Diabetes, 2016 (Accepted)

Journal of Diabetes

INTRODUCTION

At diagnosis, the majority of individuals with Type 2 diabetes are obese, experience postprandial blood glucose excursions and have a sedentary lifestyle [141] [159]. Metformin is recommended as first-line diabetes drug to reduce blood glucose in order to achieve a target of HbA_{1c} < 53.0 mmol/mol (7.0%) but is not always sufficient [170]. In many individuals, it will eventually be necessary to initiate insulin treatment to achieve the target glycemic goal.

Along with the improvement of glycemic control, weight gain is a frequent challenge in insulin treatment [171]. In the UKPDS individuals with type 2 diabetes assigned to the intensive group had an average weight gain approximately 4 kg more (3·1–4·9, p<0·0001) than the standard treatment arm [124]. Insulin associated weight gain is

problematic for several reasons. For every gained kilogram, the risk of coronary heart disease increases along with adverse changes in the patient's lipid profile and blood pressure [172–175]. Additionally, when insulin treatment is postponed due to the patients fear of gaining weight, this can also negatively affect their cardiovascular risk profile and increase morbidity and mortality [30,176]. This psychological barrier associated with insulin treatment and the accompanying weight gain can affect compliance and diabetic control. Woman especially have been reported to omit or misuse insulin to manipulate with their weight [30]. Weight gain with insulin therapy can be reduced, and being aware of the problem may help to avoid it [30,177]. Lifestyle interventions such as exercise and diet programs have the potential to counter-act insulin-induced weight gain [178]. Moreover, the type of insulin and form of therapy, surgery, and weight loss agents could be options in preventing excessive weight gain [178].

Few studies have tried to identify risk factors predict an excessive weight gain during insulin treatment among patients with Type 2 diabetes mellitus. Van Dieren et al. [179] tried to determine the baseline characteristics and glucose-lowering therapies associated with weight change in patients from the ADVANCE trial. They found that weight gain was associated with younger age, Caucasian ethnicity, smoking and higher HbA_{1c}.

If prediction of excessive weight gain was possible on an individualized level, targeted initiatives could be carried out in order to avoid or reduce this undesired insulin associated weight gain. Previously, it has been shown how simple techniques from machine learning could be successfully used in similar medical challenges within diabetes [54,112,153,159]. In this study, we investigate to what extent it is possible to predict individuals who will experience excessive weight gain during insulin treatment.

RESEARCH DESIGN AND METHODS

We used clinical available baseline data and 3-month control visit data from The Copenhagen Insulin and Metformin Therapy Trial (CIMT) [180]. Our objective was to

investigate if this information could help to identify individuals with Type 2 diabetes who would experience excessive weight gain during insulin treatment.

DATA COLLECTION

The primary objective of the CIMT trial was to evaluate the effect of an 18-month treatment with metformin versus placebo in combination with one of three insulin analogue regimens. The primary results are described elsewhere [181,182]. A total of 412 participants with Type 2 diabetes over 30 years of age were randomly assigned to metformin/placebo in combination with one of the following insulin regimens:

- Biphasic insulin aspart 30 before dinner with a possible increase to two or three daily injections.
- Insulin aspart before the main meals (three times daily) and insulin detemir before bedtime.
- Insulin detemir once daily before bedtime with a possible increase to two daily injections.

Weight, medical history and blood samples were assessed at baseline. Every 3 months during the 18-month trial, the participants were examined, and weight and blood samples collected. Table 1 shows the patient characteristics and data.

All participants provided written informed consent before participation. The protocol was approved by the regional ethical committee (region of Copenhagen journal number H-D-2007-112) and the Danish Medicines Agency (journal number 2612-3648) and was conducted in accordance with The Helsinki Declaration and guidelines for Good Clinical Practice. The overall amount of missing data used in this sub-study was low (<3%) and was handled using multiple imputation [183].

The aim of this study was not to assess the arms; in this study, the patients from each arm were pooled together.

PREDICTION MODEL

We developed a pattern classification method to predict individualized weight gain into one of two classes: small weight gain or weight loss (corresponding to 1st-3rd quartile) or excessive weight gain (corresponding to 4th quartile) during the 18-month trial.

Logistic regression classification was chosen for basis of the model due to the possibility of including both nominal and ordinal data types. Moreover, logistic regression has a transparent decision model, which makes it appealing in a clinical setting as a decision support system. We used forward selection to include features in the model based on statistical significance. Moreover, we used 10-fold cross validation to ensure that the model was not over-fitted and that the results were transferrable to a similar cohort in the clinic. Predictor candidates used for inclusion are listed in table 1.

We present and compare two instances of the classification model: (A) the 0-month model that uses baseline information, and (B) the 3-month model that uses baseline information as well as information about weight and insulin dose changes during the first three months of the trial.

CLASSICAL STATISTICAL ANALYSIS

Patient characteristics and results are presented as unadjusted mean ± (standard deviation) or median (25th; 75th percentile) as appropriate. For the purpose of testing for baseline differences between group characteristics, a two-way t-test was used for normal distributed data. A Chi-square test was used for proportions and in particular to test for difference in type of insulin regimen and insulin with and without metformin treatment between the groups.

RESULTS

A total of 412 patients were included in this analysis.

The median weight gain among the patients was 2.4 (95%: -5.6 ;12.4) kg during the 18 months. 103 patients were excessive weight gainers, defines as the upper 4th quartile, the 75% upper threshold was a weight gain of 6.2 kg or more. The weight gain range in the 4th quartile was 6.2 to 22 kg with a median of 8.9 (95%: 6.3 ;15.2). The histogram for the weight changes are seen in figure 8 (top). In the bottom of figure 8 is seen the time dependent change in weight for the two groups. Noteworthy is that for the excessive gainers the weight gain is not saturating within the first months.

The characteristics for the two groups are shown in table 6. The excessive weight gainers were at baseline on average younger with shorter duration of diabetes, with higher body weight. In addition, the group had a significant lower proportion of patients with prior insulin usage, but more patients with prior use of metformin.

There was no statistical difference in type of insulin treatment between the groups. However, less patients received metformin + insulin during the trial in the excessive weigh gain group ($P<0.001$). Still, this information was not included in the final models because it did not yield any additional and independent information.

Table 6 - Baseline characteristics and information about insulin and weight changes the first 3 months. Difference between Q1-3 and Q4 is test depending on data type and normality. Proportions is tested with chi square, normal distributed data are tested using two-sample t-test and no normal distributed are tested using Mann–Whitney U test.

		Weight	**Weight gain**	**p-value**
Baseline data	**N**	**309**	**103**	
	Average 18 month weight gain (kg) (95	**0.9 (-6.1;5.3)**	**8.9 (6.3;15.2)**	**P<0.05**
	Prior insulin usage (%)	70	54	P<0.05
	Prior metformin usage (%)	79	96	P<0.05
	Age (years)	61.8±8.4	57.4±9.4	P<0.001
	Diabetes duration (years)	12 [9;18]	10 [7;13]	P<0.05
	Gender, men (%)	69.7	67.7	NS
	Peripheral neuropathy symptoms (%)	42	22.6	P<0.05
	Retinopathy, score > 0 (%)	37	31	NS
	Autonomic neuropathy symptoms (%)	17.5	11.8	NS
	Systolic blood pressure (mmHg)	141±16	137.7±16	NS
	Diastolic blood pressure (mmHg)	82.1±10	84.3±9	NS
	Pulse (beats/min)	75.7±12.5	77.5±9.7	NS
	Microalbuminurea (%)	21.5	19.4	NS
	Macroalbuminurea (%)	4	8.6	NS
	Glomerular filtration (mL/min)	122.2±40	146.7±534	P<0.001
	Smoking (%)	15.3	18.3	NS
	Alcohol (units/wkr)	4.9±7.3	3±15.9	NS
	Weight (kg)	96.1±15.1	99.7±15.1	P<0.05
	BMI (kg/m^2)	31.9±4.2	32.6±4.3	NS
	Waist hip ratio	1±0.1	1±0.1	NS
	HbA_{1c} (%)	8.5±1.1	8.7±1	NS
	Plasma glucose (mmol/l)	10.1±3.3	11.2±3.3	P<0.05
	Total daily insulin dose (IU/day)	48.7±35.3	45.6±29.8	NS
	C-peptide (pmol/L)	824.8±547.7	1018.1±474.7	P<0.05
	Total cholesterol (mmol/l)	4.2±0.9	3.9±0.8	P<0.05
	LDL cholesterol (mmol/l)	2.2±0.8	1.9±0.7	P<0.05
	HDL cholesterol (mmol/l)	1.2±0.3	1.1±0.3	P<0.05
	Very low density cholesterol (mmol/l)	0.8±0.4	0.9±0.4	P<0.05
	Triglycerides (mmol/l)	1.8±1.1	2±1	NS
	Insulin treatment			
	▪ aspart+detemi (%)	34	34	NS
	▪ detemir (%)	35	24	NS
	▪ biphasic aspart (%)	31	42	NS
	Insulin+ metformin treatment (%)	56	34	P<0.001
	Daily insulin pr kg (IU/day/kg)	0.5±0.3	0.4±0.3	NS
3-month	3 month weight gain (kg)	0.1±2.7	3.0±3.5	P<0.05
	Daily insulin pr kg (IU/day/kg) @ 3 month	0.9±0.5	1.1±0.6	P<0.001

Baseline models performance

The ROC's for the baseline model are presented in figure 9. Significant predictors in the baseline model for the risk of excessive weight gain are: younger age, shorter duration of diabetes years, higher glomerular filtration, smoking, alcohol consumption and prior insulin usage. The c-statistics for the model are, AUC 0.68, S.E. ± 0.061.

3-month model performance

The ROC's for the 3-month model are presented in figure 9. Significant predictors included are lomerular filtration, 3 month weight gain, Daily insulin per kg. Furthermore, the gained weight the first three months is the most influencing predictor. Substantial improvements are seen from the baseline model (AUC 0.68, S.E. ± 0.061) to the 3-month model (AUC 0.80, S.E. ± 0.027) when including information of weight gain and insulin from the three month follow-up. Therefore focus will be on reporting model B in details. The 3-month-model B is presented in table 7.

Table 7 - The table illustrate the implications of using the model to screen 1000 new similar patients with two scenarios; one using a low sensitivity and another using a high sensitivity.

Screening scenario w. 1000 patients	***Sen***	***Spe***	***True positives***	***False positives***	***True negatives***	***False negatives***
Prediction after 3 months						
Cutoff with high specificity	50 %	89 %	125	83	667	125
Cutoff with high sensitivity	90 %	48 %	225	390	360	25

For example, if we choose a cutoff with high specificity from the 3-month-model and used it to predict patient with excessive weight gain. Given a sensitivity of 50% and a corresponding specificity of 89%. In a cohort of 1000 people with diabetes in

insulin treatment similar to our patients: 250 people would be excessive weight gainers and our purposed model would identify 125 of these people. In addition, the model would find 83 false positive.

If we instead choose a cutoff with high sensitivity of 90% the corresponding specificity would be 48%. If the same 1000 people with diabetes were screened that would find 225 of the excessive weight gainers and 390 false positive. This screening scenario is listed in table 7.

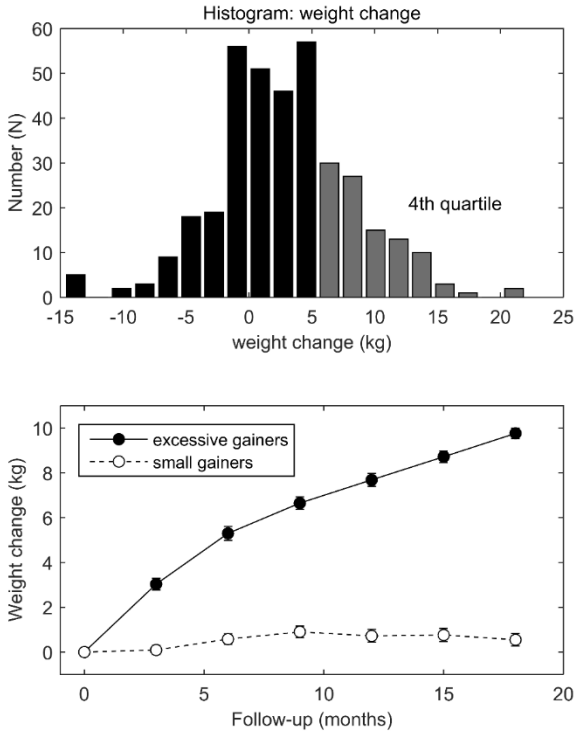

Figure 8 - The upper figure show the histogram for weight changes during the 18 months. The gray area show the 4th quartile (the participants with excessive weight gain). The lower figure show the development from each follow-up between the participants with excessive weight gain and the participants with small gain.

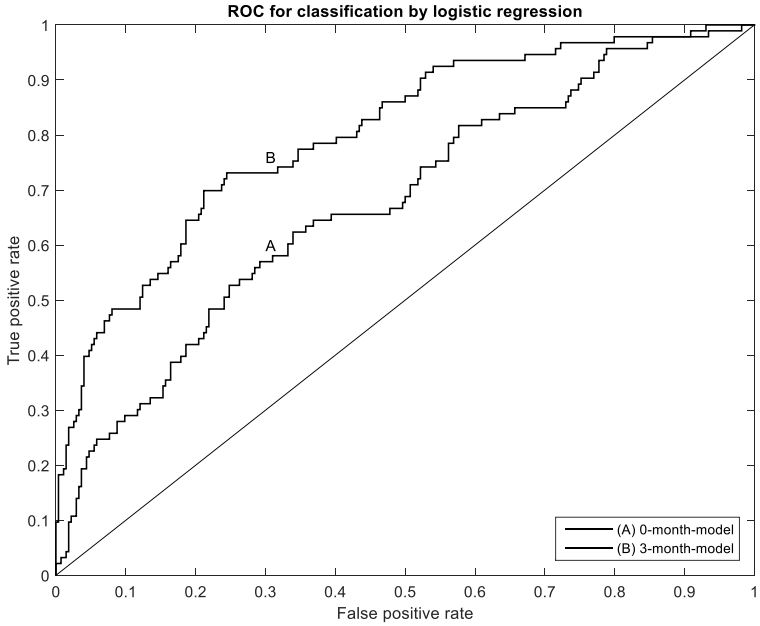

Figure 9 - Receiver operating characteristic for (A) the model using only baseline information and (B) using both baseline and 3-month follow-up information to predict excessive weight gain.

DISCUSSION

The present study highlights the clinical factors for prediction of weight gain in a cohort of individuals with Type 2 diabetes mellitus treated with insulin. Simple clinical variables may provide a clinically useful method for the prediction of excessive weight gainers in this population. Our cohort had a weight change of 2.4 kg (95%: -5.6; 12.4) during the 18 months. This observed mean weight change is similar to what has been reported from UKPDS where the mean weight change was approximately 2.6 kg over the course of 18 months [124]. The delta weight gain the first three months was the strongest contributing factor in predicting the 18-month weight gain. This finding may not be surprising as this measure provides direct feedback from the patient's weight response to the treatment. Although one-third of

the weight gain occurred in the first 3 month, it would not be preventable. It is noteworthy that the weight gains for the excessive weight gainers did not occur within the first months.
Using the 3-month information is reasonable at preventing the overall weight gain during the follow-up because the predicting accuracy is much higher compared to using only baseline information for prediction.

We found in our cohort that the group with the largest weight gain during the 18-month follow up was associated with lower percentage of prior insulin usage. This finding is in line with established knowledge that the initial treatment of insulin is related to the largest weight gain during this treatment [30]; in our study, the group with excessive weight gains were also younger, had shorter duration of diabetes and had fewer symptoms of peripheral neuropathy. These factors are connected and in line with the lower percentage of prior insulin usage. Balkau et al. [126] investigated factors associated with weight gain in people with Type 2 diabetes starting insulin treatment. They found that the main factors associated with weight gain were higher insulin dose, higher baseline HbA_{1c}, and lower baseline BMI. In our study, we did not find an association with BMI or HbA_{1c}. Nevertheless, initial weights were significantly different between the groups. Regarding HbA_{1c}, our cohort had lower initial levels than the study group from Balkau et al., which could explain why this was not a significant predictor. Pontiroli et al. [128] also investigated factors associated with insulin related weight gain. They did not find baseline HbA_{1c} as a predictor for weight gain. They also found that high insulin dose was associated with weight gain, which is also in line with our findings; daily insulin per kg (IU/day/kg) at 3 months was a highly significant ($P<0.001$) predictor for weight gain in our study. The amount of insulin prescribed was increased during the first visit (3 months from baseline) - possibly as a precaution when starting insulin treatment. This may be the reason why the baseline insulin prescribed was not a good predictor. The insulin given to each participant was continuously evaluated, but the three month doses were closely related to the average dose during the trial. This result explains why the baseline

insulin dosage was not a good predictor.

Metformin usage during insulin treatment has been seen to reduce weight gain [184,185] possibly because of lower insulin dosage needed to maintain low blood glucose [185]. In our groups, the metformin+insulin treatment proportion was also lower in the excessive weight gain group. However, this information did not provide any independent predictive information; instead, information of insulin dosage was included in the model.
Glomerular filtration rate was included in the model. This predictor did provide significant independent information but the impact of this predictor is very small (see table 2). It may be more practical if this predictor was removed from the model; however, it does provide independent information and could easily be set to an average estimated value when this information is not available in the clinic.

One limitation of our proposed model is it would yield a significant proportion of false-positive predictions, depending on the chosen level of sensitivity/specificity. However, this might not be a major problem as interventions often consist of lifestyle modifications, which have few adverse effects and would benefit false-positive cases [173]. The number of false positives must be expected when trying to separate a group based on an arbitrary threshold such as the upper 4th quartile. In future work, we need to validate the model in other populations and also show the impact of the model used clinically and that the use of our proposed prediction model eventually leads to better patient outcome [44,130].

In summary, we have demonstrated that the risk of excessive weight gain during insulin treatment may be predicted by using an algorithm that incorporates routine clinical variables and the delta weight change and insulin dosage during the first three months. Our findings extend the previous work performed in this field by developing an operable and simple model.

Given that a substantial proportion of the weight gain occurs in the first 3 months after initiating insulin therapy, a pragmatic approach would be to monitor on a monthly basis and in patients gaining more than 1 kg to start intervention in order to avoid further weight gain. In future work, the implications of implementing such model should be investigated.

SUMMARY AND PERSPECTIVES

The following section provides a summary of the thesis and a discussion of perspectives from the findings.

Detection of diabetes and its complications is important in order to start a proper treatment as early as possible. It takes years to develop long-term complications. By treating people with diabetes, it is possible to delay or minimize the long-term complications. Nevertheless, it is challenging to identify relevant patients before they develop serious complications. When patients are diagnosed with Type 2 diabetes, it is difficult to know which patients will develop which types of complications. Diabetes affects most organs of the body - from the small blood vessels to the larger macro structures such as the heart. Patients may therefore obtain complications on both cognitive function, extremities, heart, kidney, eyes, etc. Specialized treatment may be an important means to achieve the best possible individual outcome. Predictive models have the potential to help diagnosing patients and targeting proper treatment.

This PhD thesis summarizes the general use of predictive models in diabetes (**study I**) and focuses on two main areas in the use of predictive models within Type 2 diabetes.

The first part concerns the finding of latent diabetes in the common population using several types of screening approaches (**study II-III)**. The studies show that using such predictive models can help identify people with diabetes at an early stage. Our findings suggest that additional information often excluded from these type of models, can be used to increase the performance of such screening models. An extended feature search might also increase the performance compared to the more traditional developing of such models.

The second part described in this PhD thesis (**study IV**) revolves around predicting

which patients using insulin will be prone to large weight gains. The study shows how the rate of weight change is highly associated with the weight change 18-month year later. By using our proposed model, physicians might be able to screen the patients and identify a group with high incidence of excessive weight gain.

There was an overlap in the use of the methods among the three studies (**study II-IV**). Logistic regression was chosen for basis of the models due to the possibility of including both nominal and ordinal data types. Moreover, logistic regression has a transparent decision model, which makes it appealing in a clinical setting. This is a common approach when modelling in medical context (**study I**). However, it could be interesting to investigate how a different approach would influence the results. A non–linear type model might be better at modeling the relations between covariates and the dependent outcome.

Performance of the algorithms (**study II-IV**) is an important aspect of their potential usefulness in a clinical setting. If the performance is low, either many false positive or few true positive has to be tolerated. In screening for diabetes (**study II-III**) this would lead to people needing subsequent testing. Subsequent testing is expensive and time consuming for both the people being tested and the medical staff. If the model were used directly for diagnosis this could potentially lead to healthy people being wrongly diagnosed. More studies are needed to assess the cost-benefit of implementing these models. Both patient health benefits and socioeconomic factors must be taken into consideration.

In people prone to excessive weight gain during insulin treatment, (**study IV**), poor screening performance would lead to either that few people with excessive weight gain would get an intensive treatment or that too many without the need for special treatment would get the intensive treatment. Criticism regarding the performance in **study IV** has been raised. One of the proposed cut off thresholds from the ROC yields a number of “need to treat” of three. Depending on the intervention chosen for the group, this is more of an economical challenge than a patient safety issue. One

proposed treatment would be some kind of lifestyle intervention with focus on eating and fitness habits. Hence, this would benefit most patient with type 2 diabetes prone to weight gain or not.

To test the generalizability of the models, evaluation of additional datasets and datasets with different characteristics are needed. To avoid over-fitting a cross-validation approach was used in **study II-IV**. Overall, this has shown high reproducibility in a different sample from the same cohort. However, the transportability of the models has not been validated. In **study II-III**, the models have been developed based on a sample from the American population (NHANES). The American population is known to be complex both in terms of ethnicity and socio-economic conditions [186]. It is be relevant to test the models in a north European country with homogenous demographics such as Denmark. In addition, temporal transportability could be relevant to investigate if the predictors in these studies are significantly influenced over time. Temporal validation could be tested by using an earlier version of NHANES. In **study IV**, we used a sample from a Danish multicenter trial. The patients were all recruited from the capital region. One concern about the generalizability in this study is that the protocol for starting and managing insulin treatment in Type 2 diabetes might be different in other countries. The models should therefore be validated in an external cohort to ensure the transportability. We know from **study I** that in general predictive models perform worse when validated on new data. In **study II**, we compared our approach to two models from Baan et al, and Bang et al. [48,49] – the performance of our proposed model was slightly increased. This seems promising, but we cannot make solid conclusions about improvements before we validate the methods.

Implementation of the models from **study II-VI** in a clinical setting is also a noteworthy concern. **Study II** shortly discusses what the challenges related to implementing the model in a clinical setting are. Now a day almost everybody has access to mobile devices such as a smart phones or tablets. The natural thing would be to consider implementing these proposed models by using html5. Html5 has

several advantages; first, it is easy to build responsive web applications that are adaptable to the unit used for viewing the application. Second, html5 would also make it easy to port the web application to a native device application if the application should be used without internet access. Third, these applications are fast to update if required. Implementation could be accomplished by using an html5 frontend, which handles the collection of patient data and presents the result in a clear manner. The logic of the model could be implemented in JavaScript directly or if computationally heavy logic were needed the JavaScript could utilize a web service where the logic was implemented in an alternative scripting language. [187] There is no need to simplify the models when the complexity of the models can be "hidden" in the backend implementation. The user can still interact with a simple, fast to use, and intuitive user interface.

In a future perspective, what is missing is the implementation of such models (**study II-IV**) in clinical practice. Questions remain: will it affect the prognosis of these patients in a span of 10-20 year; will it increase life quality for these patients and will it increase or decrease the costs of the treatment. Screening large segments of the population is moreover a political decision. In **study IV**, idealistic, this information would help the physician and lead to proper treatment of the group prone to weight gains and as a result, the weight gains could be minimized. Realistic, specialized treatment for minimizing insulin associated weight gain is fare from effective and more research is needed to shed light upon new ways of avoiding these weight gains.

CONCLUSION

Predictive models have the potential to improve the way we make diagnosis and prognosis for patients. This PhD thesis shows how combining several information from patients in a structured way can lead to models, which can be used in a medical support system. The big question that remains to be answered is; are we ready to trust

new technology in the form of prediction models? Moreover, will it have these favorable effects as suggested by research?

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ISSN (online): 2246-1302
ISBN (online): 978-87-7112-761-4

AALBORG UNIVERSITY PRESS