Risk Assessment Models for the Development of Complications in Maltese Type 2 Diabetic Patients
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Abstract

Introduction: With the IDF Diabetes Atlas 2006 predicting a Type 2 diabetes incidence rate of 11.6% among the Maltese population by 2025, treatment differentiation between high risk and low risk patients is necessary to ensure the sustainability of such a diabetes management program.

Objectives: To identify significant predictors and develop local diabetic neuropathy (DNeurM), retinopathy (DNephM) and macrovascular (MVM) models which determine complication risk in Maltese diabetic patients.

Methods: A cross-sectional retrospective study involving 120 randomly selected patients aged 25−70 years, diagnosed with type 2 diabetes ≤ 1 year and taking metformin 500 mg, perindopril 5 mg and simvastatin 40 mg was carried out at the Endocrine and Diabetes Centre at Mater Dei General Hospital in Malta to collect data for 20 predictors. Complication risk scores were assigned to participants using a developed risk scale. SPSS® 17.0 ANCOVA regression model analyses and backward elimination variable selection method (p<0.05) were used to derive parsimonious models.

Results: 12 significant predictors were retained in the models; DNeurM includes body mass index (BMI; p=1×10⁻4), glycated haemoglobin (HbA₁c) level (p=0.00019), serum fasting triglycerides (p=0.002), alcohol abuse (No; p=0.022), systolic blood pressure (BP; p=0.041) and age (p=0.070); DNephM includes systolic BP (p=4×10⁻5), serum fasting triglycerides (p=0.001), HbA₁c level (p=0.010), albumin-creatinine ratio (ACR; p=0.040) and waist circumference (p=0.095); MVM includes systolic BP (p=3×10⁻4), serum urea level (p=0.0009), waist circumference (p=0.0012), age (p=0.006), genetic predisposition (No; p=0.026), serum urea (p=0.050) and serum fasting triglycerides (p=0.062); MVM includes waist circumference (p=1×10⁻8), systolic BP (p=0.0003), total serum cholesterol (p=0.011) and HbA₁c level (p=0.060).

Conclusion: Twelve significant predictors featured in the parsimonious models: age, genetic predisposition, alcohol abuse, BMI, waist circumference, systolic BP, HbA₁c level, serum total cholesterol level, serum fasting triglyceride level, serum urea level, urinary glucose level and ACR.

Keywords: Type 2 Diabetes; Diabetic complication; Risk assessment; Computer model; Predictor; Predictor rule; Maltese diabetic patients

Introduction

The treatment of diabetic complications in a tertiary healthcare setting poses a substantial financial burden on a healthcare system [1]. Future hospital admission costs due to long-term diabetic complications could be cut down if patients are effectively treated to improve health outcomes [2] as soon as they are diagnosed with Type 2 diabetes.

The IDF Diabetes Atlas 2006 predicts that by 2025 the incidence rate of Type 2 diabetes in Malta would have increased to 11.6% of the Maltese population [3]. Such figures could have a negative impact on the Maltese healthcare system and therefore prompt for effectiveness in the treatment of Type 2 diabetes and the prevention of its complications [4]. Unfortunately, the Maltese diabetic population is afflicted by a number of predictors that collectively work to bring about the development and progression of long-term diabetic complications [5-9]. Therefore treatment that achieves tight control of concurrent predictors in the local diabetic population is essential to decrease long-term complications [5].

Treatment differentiation between high risk and low risk patients is necessary to ensure the sustainability of such a diabetes management program [10]. Multivariate computer models utilise current clinical data to estimate the risk for future complications of an individual [11]. As a result, computer models enable a population to be classified in order of complication risk and aid clinical judgement in the assignment of intensive treatment to high risk patients [12,13].

The scope of this study was to identify predictors which significantly contribute to the risk of complication development in Maltese Type 2 diabetic patients. Once identified, significant predictors were used to develop local diabetic neuropathy, retinopathy, nephropathy and macrovascular models which determine risk for complication and consequently treatment effectiveness in early Type 2 diabetes patients.

Materials and Methods

Setting and criteria

A retrospective cross-sectional study was carried out at the
Endocrine and Diabetes Centre at Mater Dei General Hospital (MDH), Malta. There was a preference to gather data from this setting since it is a national centre for diabetes and therefore a much more local representative sample could be attained in terms of age, social stratification and spatial distribution. In addition, clinical tests and investigations at MDH are carried out and analyzed using evidence-based and validated procedures. These were consistent throughout the time period in which this study was carried out leading to less noise generation.

Data from the participants’ medical files and computerised medical records at the Endocrine and Diabetes Centre was collected over the period of October 2010 - August 2011. The most recent data available during this 10 month period was recorded in each case. The sample population comprised of 120 randomly selected patients aged 25-70 years, diagnosed with Type 2 diabetes ≤ 1 year and taking metformin 500 mg bd, perindopril 5 mg od and simvastatin 40 mg. The criteria that had to be met by patients to enable their participation in this research excluded patients younger than 25 years of age or with gestational diabetes since Type 1 and gestational diabetes were not included in this study. Patients over 70 years of age were also left out of this study since severe complications would most probably have already set in. After data collection the sample was reduced from 120 to 92 participants since the required data for certain predictors was not available in 28 cases and therefore these were excluded from the study.

**Predictor list**

Table 1 shows the 20 predictors for the risk of complication included in the study. 12 predictors were selected for diabetic neuropathy and retinopathy, 16 for diabetic nephropathy and 13 for macrovascular complications. They include laboratory test results (e.g. glycated haemoglobin (HbA1c), albumin creatinine ratio), clinical investigations (e.g. blood pressure, urinary glucose) and demographic data (e.g. age, waist circumference) which are known risk factors for complication development in Type 2 diabetes. Gender, genetic predisposition, current tobacco use and alcohol abuse were captured as dichotomous categorical variables, while proteinuria, urinary glucose and urinary albumin levels had multiple levels. The predictors chosen for evaluation reflect clinical tests and investigations that are routinely carried out in the local setting to ensure that data collection posed no difficulties.

**Study outcome**

The outcomes of this study were the development of risk assessment models based on the risk for complication development allocated to participants by resident specialists at the Endocrine and Diabetes Centre using a scale (Diabetes Complication Risk Index) devised for this purpose. Complications were classified into four: neuropathy, retinopathy, nephropathy and macrovascular complications. Consequently the four models that resulted from the analyses were termed: Diabetic Retinopathy Model (DRM), Diabetic Neuropathy Model (DNeurM), Diabetic Nephropathy Model (DNephRM) and Macrovascular Model (MVM).

**Risk assessment**

The Diabetes Complication Risk Index (DCRI) shown in figure 1 is a five-point Likert scale ranging from 0 to 4, with 0 corresponding to no risk of complication development and 4 corresponding to a very high chance of development. Its purpose was to provide a scale for the risk assessment conducted by three resident specialists at the
Endocrine and Diabetes Centre. They used their clinical judgement and the DCRI to assign a total of 4 complication risk scores to each of 40 study participants from the sample. These 4 scores individually represent the current risk for neuropathy, retinopathy, nephropathy and macrovascular complications of that particular participant.

Inter-rater reliability testing was concurrently carried out using correlation analysis to ensure that the DCRI was an appropriate tool for risk assessment. An acceptable degree of homogeneity was found when the complication risk scores assigned by each resident specialist were compared to that of the other raters. Once inter-rater reliability was established, one resident specialist continued the risk assessment for the rest of the participants.

Ethical considerations

This study was approved by the University of Malta Research Ethics Committee in Msida, Malta. Authorisation to view patient medical files and computerised records was obtained from the Endocrine and Diabetes Centre, as well as the Information Management and Technology Department at MDH, Malta. The principles of the Helsinki Declaration on Research Involving Human Subjects were followed when conducting this research and written informed consent was obtained from all participants involved in the study.

Data processing and analyses

Bivariate Pearson correlation (p<0.05) was utilised to determine whether inter-rater reliability was achieved for the risk scores assigned by means of the DCRI. The data was then modelled using ANCOVA regression model analyses on SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA) for Windows. A backward elimination variable procedure was conducted to eliminate weak predictors that contributed marginally in explaining variation in the risk scores. The parsimonious model included solely significant predictors; however a few predictors whose p-values exceeded the 0.05 level of significance marginally were retained in the model fit. A regression coefficient (B) is the change in the risk score per unit increase in the predictor value. In other words, it is the weighting assigned to a significant predictor to describe its contribution to the risk for complication development. Studentized residuals were used to identify outliers; Cook’s distances were used to identify influential observations and residual plots, displaying studentized residuals against predicted values, were used to identify model oddities.

Results

A statistically significant positive correlation was obtained between the scores assigned by 3 three resident specialists (Pearson correlation=0.888, 0.844, 0.812), indicating good inter-rater reliability for the DCRI.

Significant predictors

The significant predictors that featured in the parsimonious models were age, genetic predisposition, alcohol abuse, BMI, waist circumference, systolic BP, HbA\textsubscript{1c} level, serum total cholesterol level, serum fasting triglyceride level, serum urea level, urinary glucose level and albumin-creatinine ratio.

Most of these variables featured in more than one model, with most of them being very strong predictors. In fact, systolic BP was the strongest predictor of nephropathy (p=3×10\textsuperscript{-6}) and retinopathy (p=0.0004), and also featured in macrovascular complications (p=0.0003) and nephropathy (p=0.041). BMI was the strongest predictor of neuropathy (p=0.0001), while waist circumference was the best predictor of macrovascular complications (p=1×10\textsuperscript{-6}) and also a strong predictor of nephropathy (p=0.0012) and retinopathy (p=0.095). HbA\textsubscript{1c} level was the second strongest predictor in neuropathy (p=0.00019) and also a strong predictor of retinopathy (p=0.010) and macrovascular complications (p=0.060). Serum fasting triglyceride level was also the second best predictor of retinopathy (p=0.001) and a strong predictor of nephropathy (p=0.002) and nephropathy (p=0.062).

Diabetes complication models

Table 2 shows the predictors present in the parsimonious models and their regression coefficients ranked by their contribution in explaining total variance of the dependent variables. The regression models identified six significant predictors in the DNeurM, five predictors in DRM, eight predictors in DNeprM and four predictors in MVM.

The parsimonious models for the complications explained 73.3%, 67.0%, 81.8% and 62.9% of the total variance of DNeurM, DRM, DNeprM and MVM respectively. These R-squared values compare well with those of corresponding full models that accounted for 74.1% (DNeurM), 70.1% (DRM), 83.5% (DNeprM) and 66.3% (MVM) of the variability of models. This implies that the exclusion of the weak predictors from the model fit had minimal effect on the goodness of fit.

Although p-values for age (p=0.070) in DNeurM, waist circumference (p=0.095) in DRM, serum fasting triglycerides (p=0.062) in DNeprM and HbA\textsubscript{1c} level (p=0.060) in MVM exceed the 0.05 level of significance, they was included in the model fit because their contribution was found to be considerable on the corresponding R-squared value.

In each model fit, the proportion of studentized residuals exceeding the ± 2 threshold values was around 5% which conforms to what is expected. Cook’s distances were comparable, indicating no influential observations. Moreover the residual plots displayed no curvature indicating no anomalies and misspecifications.

The DNeprM regression output presents some contrasting results with literature. From the analyses, a decrease of 0.296 in the DNeprM risk score resulted for the presence of trace urinary glucose when an increase in the risk was expected. Similarly, a decrease of 0.171 was obtained for the presence of 3+ urinary glucose. In addition, since the increase in the risk score associated with + urinary glucose is of 0.183, the detection of 2+ urinary glucose was expected to cause a larger increase in the risk score than the resultant 0.149 increase. These conflicting results may be attributed to the small sample sizes of urinary glucose levels trace (n=2), +1 urinary glucose (n=20), +2 (n=12), +3 (n=13) and +4 urinary glucose (n=4).
nephropathy ($p=3\times10^{-7}$), study outcomes show that systolic BP was more associated with nephropathy and macrovascular complications ($p=0.0003$). Such relationships are consistent with other research observations that suggest a decrease in the risk for nephropathy [23-27] and macrovascular complications [28-30] with better systolic BP control.

The BMI has also been associated with macrovascular complications [31]. However, in this study, the BMI only appeared as the strongest predictor in the parsimonious model for diabetic neuropathy ($p=0.0010$). Since the BMI is implicated in the formation of atherosclerosis [21], correlation with neuropathy is plausible although the non-significance of the BMI in the best MVM requires further elucidation.

**Metabolic syndrome**

The main four predictors are components indicative of the metabolic syndrome, which the IDF defines as the concurrent presence of central obesity together with either two of high triglyceride levels, high BP, low HDL cholesterol levels and 'Type 2 diabetes' [32]. They suggest that effective management of the metabolic syndrome, for which the sample population was being treated, results in a better complication prognosis. In fact, there is a strong association between the metabolic syndrome and the development of chronic complications in patients with Type 2 diabetes [33,34].

**Mean complication risk**

Even though the objective of pharmaceutical treatment in Type 2 diabetes is to concurrently manage co-existing conditions, in clinical practice, a significant amount of patients still do not meet the treatment goals [35]. Nevertheless, the mean risk scores was obtained by the sample population, using the DCRI, ranged between 1.04 and 1.28 (minimum risk score 0.3; maximum risk score 4). According to the DCRI this indicates that, on average, participants had a mild risk for complications because the predictor means suggest that most patients were either within or only slightly outside the recommended target levels. Therefore early treatment in local diabetic patients is effective although not optimal. Timely introduction of new drugs to the regimen and ensuring that medication is well titrated could easily lead to better clinical outcomes and less future morbidity.

Since cardiovascular disease is the main source of ailment and death in diabetes [7] and is closely linked with the metabolic syndrome [36], it was expected that the sample population would achieve a high risk for macrovascular complications. In fact, the highest mean risk score for complications was achieved for MVM (mean 1.28).

**Models limitations**

Although the models demonstrate the significance of several known risk factors, the parameter estimates derived from the regression models are not adequate enough to substitute clinical judgment, which also takes into account clinical experience. The predictive power of a regression model depends heavily on the sample size. The major limitation of analyzing a small data set is that strong predictors may not be found significant when fitted into a regression model that accommodates a large number of explanatory variables. It is very likely that a small sample would yield less significant predictors; hence better inferences about a population are made when using a larger sample. In other words, the predictive power of a regression model decreases considerably when the number of parameter estimates is comparable to the number of observations (sample size).
Long-standing undiagnosed type 2 diabetes results in the presentation of a more severe condition on first diagnosis compared to cases of recently developed Type 2 DM. Such patients would have already deteriorated with regards to their condition. Complications which may have been present at the time of diagnosis have not been excluded from this study. Since established models should only reflect the risk of diabetic complication development in patients who were diagnosed early on in the condition, this may have affected the predictor values and therefore limits current models.

Ideally long-term follow-ups are carried out to internally validate model results with respect to complication risks. However, since the models only project the risk of complication with a particular medication regimen, it was not possible to evaluate the model outcomes as treatment changes frequently occur.

In conclusion, diabetes-specific models which stratify the diabetic population according to the risk for complications were derived. Results emerging from this study propose that certain predictors may be more suggestive of the assessment of the risk for complications. Provided that treatment adjustments are made periodically, careful monitoring of these risk factors would be indicative of the effectiveness of the implemented diabetes management program. Even though this study provides preliminary evidence that the models could aid healthcare professionals identify the need for intensive treatment in high-risk diabetic patients, further studies and long-term follow-ups are required to improve and validate the models such that adequate risk assessment tools for primary complication prevention are obtained.

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