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Abstract

Diabetes as an unprecedented epidemic is spreading all around the world. While one in every seven health care dollars in USA is spent on diabetes, 60% of direct costs and almost 80-90% of indirect costs of that are related to diabetic complications. The ultimate aim of this study is to develop a rule-based model for advising the risk of chronic diabetic complications. An extensive literature review has been carried out to gather actual knowledge about diabetic complications and their related predisposing factors. NViv08 is used to organize and categorize the acquired knowledge. A rule-based decision support model is constructed from the obtained knowledge. CLIPS is used to represent and implement the rules and build a knowledge based decision support system.

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A KNOWLEDGE-BASED RISK ADVISOR MODEL FOR CHRONIC COMPLICATIONS OF DIABETES

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Abstract

Diabetes as an unprecedented epidemic is spreading all around the world. While one in every seven healthcare dollars in USA is spent on diabetes, 60% of direct costs and almost 80-90% of indirect costs of that are related to diabetic complications.

The ultimate aim of this study is to develop a rule-based model for advising the risk of chronic diabetic complications. An extensive literature review has been carried out to gather actual knowledge about diabetic complications and their related predisposing factors. NVivo8 is used to organize and categorize the acquired knowledge. A rule-based decision support model is constructed from the obtained knowledge. CLIPS is used to represent and implement the rules and build a knowledge based decision support system.

Keywords: Computer assisted decision making, Diabetes-related complications, Rule-based decision support system, Knowledge representation, Knowledge mining.

1 INTRODUCTION

Diabetes has been well studied, and many of the complications can be prevented. Since it is a multi-factorial disease, regulated by multiple genes and different environmental factors, which do not follow any simple model of inheritance, using information technology and in particular the application of decision support systems could be of the most important methods of reducing the heavy burden of this disease on the society (Celler et al. 2003).

Decision support systems (DSS) will assist clinicians in maximizing quality of healthcare and patients to understand more of their health. A decision model of diabetes will involve understanding the epidemiology of diabetes, diabetes pathophysiology, using of diabetes data meta-analysis, diabetes metadata classification and rules and the development of a reasoning engine.

There is a long history of DSS including different broad-based systems in the medical domain. several decision support systems are available in more specific domains of medicine. However, no such decision support system exists for the diabetes domain.

In this study, a decision support model is used to build a rule-based system to assist physicians in evidence based medicine. The developed model in the system is able to represent up to date literature and individualized patient data for patients tailored decision making.

2 METHODS

Available knowledge about diabetes and its complications were gathered from peer reviewed publications on clinical trials, meta-analysis, the Cochrane review from Medline, Cinahl, federated database searches and diabetes management guidelines published from 1995 to 2009. Keywords were integrated with appropriate combinations of:

- Diabetes or chronic disease and (Prevention or Management)
- Indicator or Indices and (Diabetes complications or Disease management)
- Morbidity or Prevalence and (Diabetes or Diabetes complications)
- Secondary prevention and (Diabetes or Medical/Health informatics)
- Medical/Health informatics and (Diabetes or Chronic disease)
- Data mining or Knowledge discovery or Data retrieve and (Diabetes or Diabetes complications)
- Predictor or Predictive tool or Predictive system and (Diabetes or disease management)
- Decision support/Expert/Knowledge based system and (Diabetes or disease management)
- Care reminder system and (Diabetes or Decision support system or Medical/Health informatics)
- Reasoning engine and (Diabetes or Chronic disease management)
- Electronic medical record or Electronic disease registry or Electronic patient record and (Diabetes or Prevention or Decision support system/Expert system/Knowledge based system)

Afterwards, having scanned the abstracts of nearly 980 primitive results, about 220 most likely related subjects have been chosen and subsequently ranked by 4 criteria in 2 different aspects of study: "Diabetes in general OR its related complications" and "DSS in general OR its related technical aspects". The inclusion criteria are shown in Figure 1.

Article ID	DSS related Introduction and definitions	Diabetes related Introduction and definitions	DSS related Technical discussions	Diabetes related Complications discussions	sum
Overall scoring	0-4	0-4	0-4	0-4	0-16
Including conditions	(>= 1 AND >= 1)				
			OR >= 1		
				OR >= 1	

Figure1. Ranking table and including criteria to review articles

The results from this review work were coded in Nvivo8 to discover associations and themes among the diabetes predisposing factors and its complications. A knowledge base including rules was developed in this phase of study. The rules in the knowledge base were fed into CLIPS (C Language integrated production system) to develop the reasoning part of a decision model for the secondary prevention of diabetes. CLIPS has been chosen in this study because of its simplicity, speed and capability to work with certainty factors and fuzzy concepts.

3 RESULTS

Diabetic chronic complications are mostly produced based on the destructive consequences of chronic blood glucose elevation on the internal blood vessels covering cells (endothelial cells). Depending on the size of involved vessels, it can be divided into two categories: microvascular disease, due to damage to small blood vessels (in the vision system (diabetic retinopathy), neural system (diabetic neuropathy), and renal system (diabetic nephropathy) and macrovascular disease, due to damage to the arteries (cardiovascular diseases mainly confined to coronary artery diseases heading to myocardial infarction, stroke and peripheral vascular diseases). There are some other kinds of complications mostly because of combinations of these two.

The predisposing factors related to diabetes complications are divided into diabetic related factors (containing diabetic control by investigating HbA1c (Haemoglobin A1c), duration of disease and type of diabetes); behavioural elements (smoking, alcohol consuming, etc.); using medications; patient's individual factors (age, sex, etc.) and having other contemporary diseases or conditions, particularly other diabetic microvascular problems.

Associations linking these two (predisposing factors vs. chronic complications) are extracted from the related literatures by applying in Nvivo8 (a qualitative data analysis computer software package produced by QSR International).

3.1 A Knowledge-based model for complications

The analysis work through Nvivo8 was conducted to identify several themes. At the starting point, an inclusive list of diabetes complications and their correlated predisposing factors were derived from the existing text books of endocrinology and other reviewed articles, respectively. Both diabetes chronic complications and diabetes predisposing factors have been classified hierarchically by 27 and 45 nodes, in that order. The two are connected by nearly 126 relationships, categorized in three different types, namely 'is a cause for', 'prevent from or decrease' and 'are the same'. All these nodes and relationships are supported by more than 280 paragraphs (facts) of 40 different sources (Table 1).

Since it is impossible to paraphrase all details in here, the relationships between blood sugar (HbA1c) and blood pressure (BP) control as two of the most important predisposing factors and all interconnected diabetes chronic complications are illustrated in Figures 2 and Table 2.

The quality of blood glucose control (for a 3-month period of time) can be deliberated by HbA1c. Having a good history of HbA1c level does prevent or decrease the risk of around 10 nodes in the diabetes chronic complications tree. On the contrary, mismanaging of that is a cause for the higher prevalence of 12 problems; meanwhile, there are 6 common complications between these two groups, which can be worse or better related to quality of blood glucose management. These relations dispersal are 7 for 'prevent or decrease' and 12 'is a cause for' with 3 intersections in the case of patient blood pressure control; that is even more complicated here in view of the fact that some diabetes complications can affect the blood pressure level while those are sometimes impressed with hypertension by themselves, as well.

With the intention of further exemplifying, Figure 3 illustrates the relationships between HbA1c and blood pressure control as two predisposing factors and diabetes nephropathy (including its component microalbuminuria and albumin excretion rate-AER level) as a diabetes chronic complication. All 3

Risk Factors and Predictors				Chronic Complications																				
				Macro vascular			Microvascular						Others											
				CVD ¹	PVD ²	CAD ³	Nephropathy	Neuropathy		Eye diseases		Infectious diseases	Genitourinary diseases	Amputation & Ulceration	Mortality	Gastrointestinal diseases	Glaucoma	Dermatologic diseases	Cardiomyopathy	Cataract				
								Autonomic	Sensory Motor	Macular edema	Retinopathy													
																							NP ⁵	P ⁴
A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S						
				Diabetes factors																				
				Other diabetic chronic complications																				
				Individualized/genetic factors																				
				Behaviour																				
				Relative diseases - conditions																				
				Drugs																				

Table 1. A cross table of diabetes predisposing factors and its chronic complication

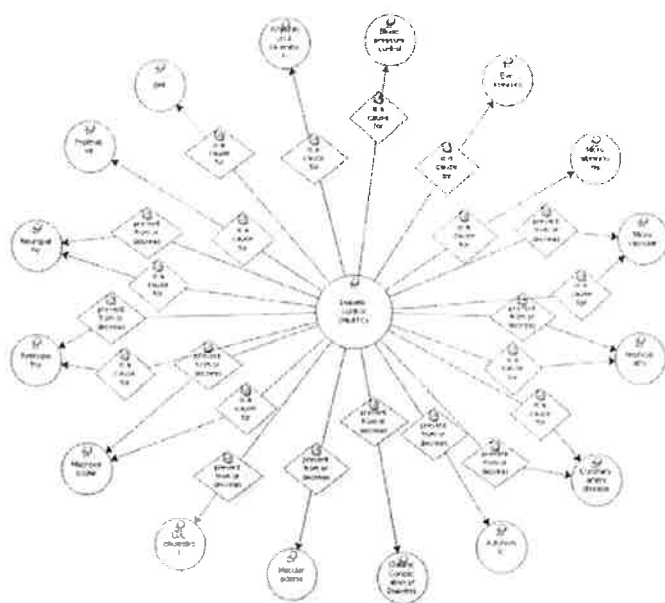


Figure2. Relationships between diabetes control (HbA1c) and diabetes complications

Author/Name of study	Type of study	Supported relationships based on Table 3
William's CHAPTER 32	Textbook	(31I), (31J), (31D), (31H), (31C)
UKPDS 38	Randomised controlled trial, n=1148, duration: 8.5 years	(31I), (31J), (31D), (31H), (31R), (31A)
Dorsey R R	Systemic review	(31I), (31J), (31D), (31H), (31C), (31M)
Klein et al.	Population-based study, n=765, duration: 10 years	(31D), (31,3), (31,13), (31,1)
Bhuripanyo et al.	Cross-sectional study, n=2060	(31I), (31J), (31A), (31C)
Al-Futaisi et al.	Cross sectional study, n=261	(31,6)
Klein et al.	Population-based study, n=996	(31I), (31J)
Krolewski et al.	Randomised controlled trial, n=89, duration: 15 years	(31D)
Kostraba et al.	Cross-sectional study, n=657	(31I), (31J)
Fujisawa et al.	Cross-sectional study, n=294	(31I), (31J)
Mogensen et al.	Population-based study, n=44, duration: 7 years	(31D)
Perkins et al.	Population-based study, n=386, duration: 6 years	(31,6)
Hovind et al.	Prospective cohort study, n=286, duration: 18 years	(31,6)
Mogensen et al.	Population-based study, n=6, duration: 6 years	(31D)
Gaede et al.	Randomised controlled trial, n=160, duration: 7.8 years	(31N)
Parving	Systemic review	(31D)

Table 2. Supporting sources of relationships between BP control and diabetes complications

different kinds of defined relationships are recognized in this figure: 9 'is a cause for', 2 'prevent from or decrease' and one 'are the same'. While both HbA1c and blood pressure control qualifications can cause and prevent diabetic nephropathy in patients, at the same time, HbA1c can directly affect on patient blood pressure. Furthermore, diabetic nephropathy can cause hypertension in the patient by itself. Based on the coded references in Nvivo8, 76 facts through the 19 related sources have been linked to these relationships.

Some of these facts which have to be written as CLIPS rules will now briefly be reviewed:

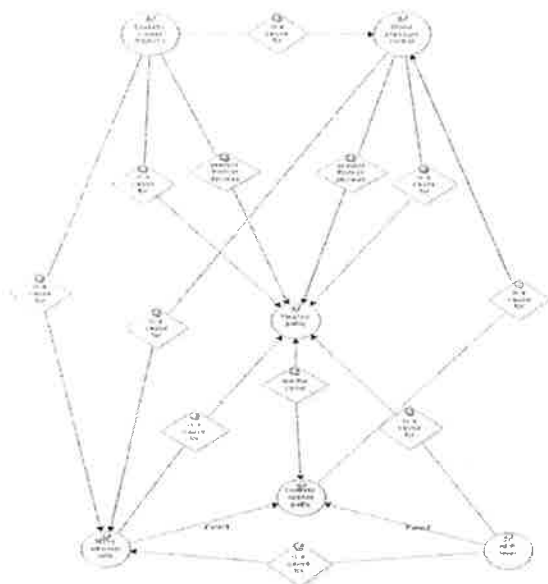


Figure 3. Relationships between HbA1c, blood pressure control and nephropathy

Around one third of diabetic patients develop persistent microalbuminuria within 20 years of onset of type1 diabetes (Hovind et al. 2004). There appear to be no substantial differences between patients with type2 and those with type1 with respect to the initiation, progression, and treatment of diabetic nephropathy (Parving 1998); however, the risk reductions seem proportional given the HbA1c differences 34% for albuminuria in The United Kingdom Prospective Diabetes Study (UKPDS) and 54% in The Diabetes Control and Complications Trial Research (DCCT) (UKPDS33 1998).

Microalbuminuria was said to confer a 60 to 85 percent risk of the development of overt proteinuria within 6 to 14 years (Bruce 2003). Without specific interventions, 20–40% of type2 diabetic patients with microalbuminuria progress to overt nephropathy (Al-Futaisi et al. 2006). The estimated risk of microalbuminuria is 3.41 cases per 100 patient-years at an HbA1c of 8%; 2.35 at an HbA1c of 7%; and 1.53 at an HbA1c of 6%. When compounded over a 9-year follow-up period, these hazard rates correspond to 26% cumulative incidence of patients developing microalbuminuria when held at an HbA1c of 8% over 9 years, versus 19% at an HbA1c of 7%, and 13% at an HbA1c of 6% (DCCT 1996). Type1 patients whose intensive insulin therapy resulted in HbA1c levels 2% lower than those receiving conventional insulin therapies had a 54% lower incidence of nephropathy (Kronenberg et al. 2008). In patients with type1 diabetes and overt proteinuria, aggressive blood pressure (BP) reduction reduced proteinuria by up to 50% (Kronenberg et al. 2008). A 10 mm Hg increase in mean arterial blood pressure, was one of the significant predictors for the development of persistent microalbuminuria (Hovind et al. 2004). In the UKPDS, a reduction in BP from 154 to 144 mm Hg was associated with a 30% reduction in microalbuminuria.

A concise schema regarding the aforementioned process is illustrated in Figure 4.

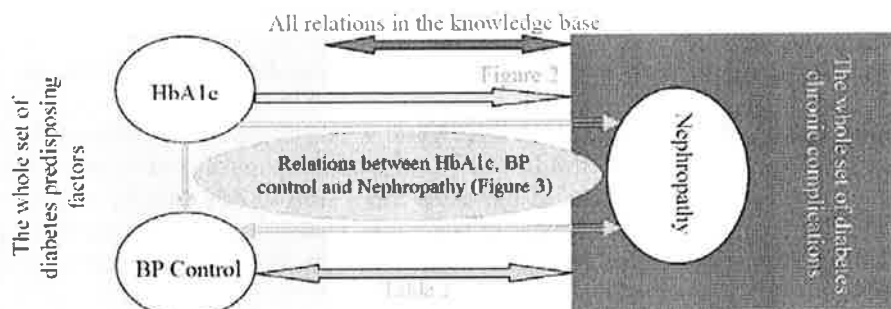


Figure 4. A schema regards to the process of making knowledge base

3.2 Authoring the Rules

The next step is transferring all facts to the rules in CLIPS. To give a better perception about how the rules in the CLIPS knowledge base work, consider an example that is extracted from above fact list:

“In type1 diabetes, each unit increase in HbA1c while $6\% < \text{HbA1c} \leq 10.1\%$, adds 3% to chance of nephropathy; and for every one unit HbA1c less than 6%, the risk decrease by 3%.”

This fact will be transferred to CLIPS rules (Figure 5) and will be tested by the data from four cases to demonstrate the results. (Figure 6)

```
(deftemplate patient-data "An example template"
  (slot name (type STRING))
  (slot type-of-diabetes (allowed-symbols Type-1 Type-2))
  (slot HbA1c (type NUMBER) (range 5 20))
  (slot risk-of-nephropathy (type NUMBER) (default 0))
  (slot has-been-test (allowed-symbols NO YES) (default NO)))

(defacts patient-list "An example fact list"
  (patient-data (name "Joe") (type-of-diabetes Type-1) (HbA1c 14) (risk-of-nephropathy 10.0))
  (patient-data (name "Bob") (type-of-diabetes Type-2) (HbA1c 10) (risk-of-nephropathy 10.0))
  (patient-data (name "Sue") (type-of-diabetes Type-1) (HbA1c 9.7) (risk-of-nephropathy 10.0))
  (patient-data (name "Jack") (type-of-diabetes Type-1) (HbA1c 5) (risk-of-nephropathy 10.0)))

(deffunction nephropathy-risk-calculation "An example function"
  (?a ?b)
  (+ ?b (* 3 (- ?a 6))))

(defrule HbA1c-nephropathy "An example rule"
  ?f1 <- (patient-data (name ?name)
    (type-of-diabetes Type-1)
    (HbA1c ?x &: (<= ?x 10.1))
    (risk-of-nephropathy ?y)
    (has-been-test NO))
  =>
  (bind ?new-y (nephropathy-risk-calculation ?x ?y))
  (modify ?f1 (risk-of-nephropathy ?new-y) (has-been-test YES))
  (printout t ?name " has " ?new-y " percents risk of nephropathy." crlf))
```

Figure 5. An example of a rule in CLIPS knowledge base

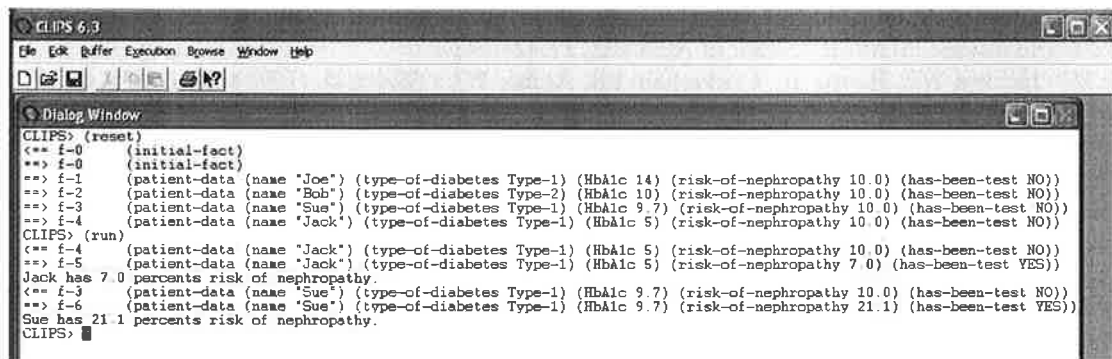


Figure 6. Changing the risk of nephropathy in target cases after running CLIPS

4 DISCUSSION AND CONCLUSION

The developed knowledge-base model in this study confirmed that diabetes is regulated by various multiple factors which do not follow any simple model of inheritance; hence, risk advisor system could be of the most important methods of prediction and consequently prevention of its chronic complications heavy burden.

There are several projects in Australia focusing on diabetes research. The Australian Diabetes obesity and lifestyle study (AusDiab) and Fremantle diabetes study are some examples that extensively focus on diabetes management. These studies focused on modifiable risks and their effects on diabetes outcome in general. In addition, there are some computerized information systems related to diabetes such as measuring blood glucose level and the calculation of insulin dosage, a system that sends SMS

reminders for diabetes patients, a multimodal reasoning system for diabetic care (Montani et al. 2000), diabetic foot advisor (Awad & Tremaine 2000) etc.

Currently, there is no decision support system for secondary prevention of diabetes that is based on a model focusing on relationships between diabetic modifiable risk factors and its complications individually.

It can be seen that acquired knowledge in this model has been derived through an extensive literature review of epidemiological data in the domain; despite the fact that earlier expert systems in medicine cover narrow medical domains, or relying from expert opinions only (Spooner 2007).

The decision support model of this study can be used to inform diabetic patients about the risk and severity of probable complications, help health advisors to convince patients to change their lifestyle, and to inform healthcare providers to design immediate preventive interventions before a patient loses her/his capability.

The complete decision support model is heading for evaluation with real data of former studies on diabetes to determine prediction accuracy of the risk in different groups of patients and for each diabetic complication individually. Further work will be planned to integrate the system with existing patient databases, assess acceptance rate of the system by experts and updating the knowledge base of the model.

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