Assessment of diabetic macrovascular complications: a prediabetes model

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ABSTRACT

Prediabetes is a condition that requires early intervention against diabetic macrovascular complications. This study aims to assess whether or not the likelihood of diabetes macrovascular complications occurring in prediabetes can be better estimated by a model combining a set of conventional and emerging biomarkers, with a view to improving cardiovascular disease (CVD) screening in individuals with elevated blood glucose levels associated with prediabetes. A total of 71 participants (female/male: 32/39) were divided into two groups – the prediabetic group (preDM: n=34) and the diabetic with cardiovascular complications group (DM+CVD: n=37). Blood glucose level (BGL), blood pressure (BP), total cholesterol (TC), high-density lipoprotein (HDL) and TC:HDL ratio, erythrocyte oxidative stress (as determined by reduced glutathione [GSH], malondialdehyde and methaemoglobin levels) and vascular events (D-dimer, homocysteine and whole blood viscosity) were measured. Statistical analysis was by binomial logistic regression modelling with forward likelihood ratio step procedures. A combination of BGL, BP, erythrocyte GSH and TC gave the best group identifications, with 28/34 (82.4%) and 29/37 (78.4%) members correctly identified in the preDM and DM+CVD groups, respectively. Six of the 34 (17.6%) prediabetes individuals were logistically identified as having diabetic macrovascular complications, but clinically did not qualify for CVD intervention under current screening models. The authors propose that a combination of BGL, BP, erythrocyte GSH and TC can provide a clinically acceptable standard for identifying CVD risk in individuals with prediabetes. This model provides a tool for early identification and targeted intervention in individuals with subclinical diabetes who are at risk of CVD.

KEY WORDS: Diabetic vascular complications.
Heart diseases.
Mass screening.
Prediabetic state.

Introduction

As the incidence of diabetes mellitus (DM) increases so, too, do its cardiovascular complications, which are the leading cause of morbidity and mortality in persons with DM.[1,2] In the heart failure classification and management guidelines of the American College of Cardiology and the American Heart Association, the concept that cardiovascular disease (CVD) is progressive and that predisposing conditions such as diabetes are preventable by early identification and intervention is reinforced.[3] The onset and/or progression of diabetic macrovascular complication can be prevented or delayed if an early diagnosis of DM is made.[4] Hence, it is currently recommended that DM patients be screened regularly for early identification of CVD including coronary artery disease (CAD).[5]

In Australia, an estimated 10% of all adults have impaired glucose tolerance,[6] which predisposes them to substantially increased cardiovascular risk,[7–9] in addition to developing diabetes. The predisposition is perhaps due to an ongoing, but unmanaged, hyperglycaemic toxicity.[10,11] Identification of those individuals with increased risk of developing diabetes and associated cardiovascular disease based on blood glucose level (BGL) has the potential to initiate appropriate early interventions as well as reduce healthcare costs and improve quality of life.[12,13] It has been reported that use of two or more risk factors of the current screening programmes to identify individuals with subclinical CAD did not help to identify asymptomatic patients and that such criteria are only related to a more severe CAD.[14–16] This has prompted the current investigation to determine the emerging risk factors, including erythrocyte oxidative stress (EOS) and associated vascular event indices,[17] in an attempt to improve the risk stratification of individuals with preclinical diabetes.

Currently, two models are in use for the assessment and management of cardiovascular risk in diabetes. One is a flowchart[18] based on the Framingham Heart Study. It uses a combination of traditional risk factors including diabetes diagnosis, gender, left ventricular hypertrophy and smoking status as categorical variables; and age, systolic blood pressure and total cholesterol (TC):high-density lipoprotein (HDL) ratio as continuous variables. The other is the New Zealand Guideline Group (NZGG) model,[19] which also uses diabetes diagnosis, gender and smoking status as categorical variables; and age, diastolic and systolic blood pressure readings and TC:HDL ratio as continuous variables. Common to both models is that diabetes and

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smoking status are categorical variables. By such usage, the models omit those individuals with elevated BGL, which is synonymous with undiagnosed diabetes (≥7.0 mmol/L) and prediabetes (≥5.6 mmol/L).[9,11,20] Moreover, the non-smokers among this portion of the population may also be suffering hyperglycaemia-induced oxidative stress,[21] which is similar to that occurring in smokers.[22]

Under current guidelines, follow-up is recommended for those individuals who smoke, have known impaired glucose tolerance or impaired fasting glucose. This suggests that prediabetes has been recognised as a factor underlying cardiovascular complications in diabetes progression.[12] However, the current risk assessment for CVD in DM as provided by the Framingham Heart Study and the NZGG models does not identify a significant portion of those at real risk or those with subclinical CVD.[14,16] A high BGL (5.6–6.9 mmol/L) is synonymous with prediabetes, which quite commonly precedes diabetic macrovascular complications, but these risk assessment models do not include BGL as a criterion.[7] Furthermore, smoking is considered a risk factor because it induces oxidative stress,[23,24] but the hyperglycaemia-induced oxidative stress in non-

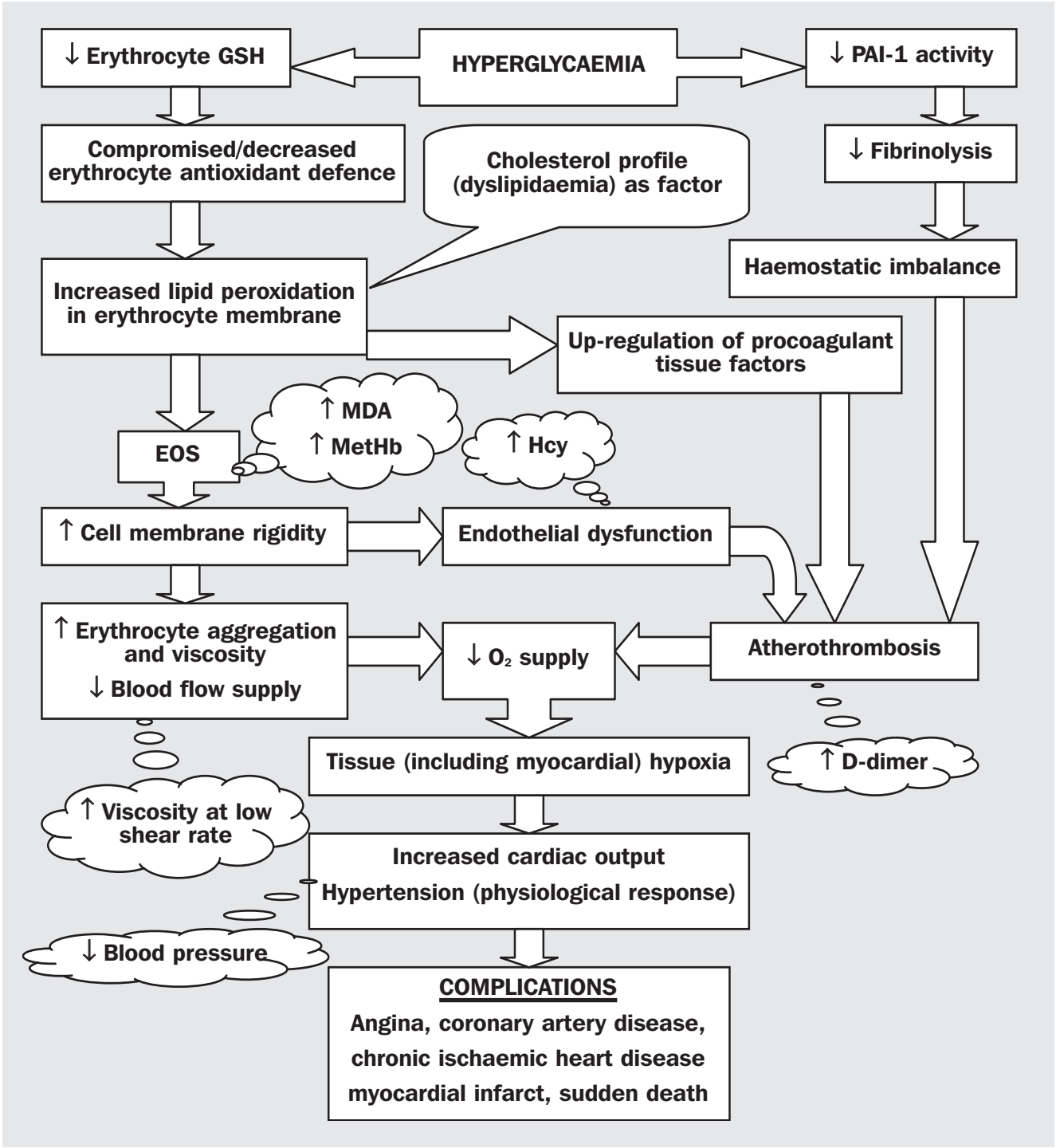

Fig. 1. Illustration of diabetic macrovascular pathways involving the erythrocyte.
EOS: erythrocyte oxidative stress, Hcy: homocysteine, PAI-1: plasminogen activator inhibitor-1.

smokers seems to be ignored in the screening programmes.

Although traditional screening models have greatly improved risk prediction,[16] studies have shown that a considerable number of future cardiovascular events occur in individuals with only one (or no) risk factor present.[14–16] Interestingly, emerging laboratory parameters that hold promise as risk predictors for macrovascular clinical events include oxidative stress indices, (antioxidants and lipid peroxidation indicators),[25–28] and macrovascular event indices (endothelial dysfunction, hypercoagulability and stasis, respectively, indicated by homocysteine, D-dimer and blood viscosity).[16,29–32] Nevertheless, different parameters reflect different pathophysiological pathways and do not necessarily apply to all disease processes.[28]

There are two main pathways to diabetic macrovascular complications. Hyperglycaemia and insulin resistance enhance the synthesis and secretion of plasminogen activator inhibitor and thus decrease fibrinolysis. The manifestation can be atherothrombotic coagulation-fibrinolysis imbalance. Hyperglycaemia also leads to increased glycolysis and depletion of the antioxidant reserve. In the erythrocyte, EOS follows the depletion of reduced glutathione (GSH). Associated with EOS is up-regulation of procoagulant tissue factor and decreased erythrocyte membrane fluidity. Increased blood viscosity, of which decreased erythrocyte membrane fluidity is partly a contributing factor, is associated with an increased risk of vascular events (Fig. 1).[33]

The authors hypothesise that using BGL, as a continuous variable, together with the determination of oxidative stress markers (erythrocyte GSH, malondialdehyde [MDA] and methaemoglobin [metHb]) will provide greater accuracy for assessment of risk of future CAD, compared to the current assessment models, especially for those with elevated BGL but not diagnosed with diabetes. The purpose of this study is to determine the feasibility of employing BGL and known markers of EOS to develop a separate model to assess the risk of future diabetes and cardiovascular co-morbidity among individuals with prediabetes status. The rationale for biochemical parameters tested in this study is strictly hyperglycaemia-induced EOS pathophysiology associated with hypertension (Fig. 1).

Materials and methods

The study, approved by the Ethics in Human Research Committee of Charles Sturt University, was part of an evaluation of EOS in diabetes and its cardiovascular complications project.

Volunteer recruitment and baseline data

A total of 620 volunteers, from the twin cities of Albury (NSW) and Wodonga (Victoria), Australia, participated in the project. All volunteers consented to participate in the research. The selection criteria and grouping were as previously published.[34] A further exclusion criterion in this study was any participant with an incomplete data set. Seventy-one participants (female/male: 32/39) were selected for this study, which constituted two groups: prediabetes (preDM; n=34) and diabetes with cardiovascular complication (DM+CVD; n=37).

Prediabetes in the study was defined as a state of undiagnosed diabetes that presents a BGL of 5.6–6.9 mmol/L (fasting) or 5.5–11.0 mmol/L (random). The BGL in this definition was based on the recommendation contained in the position statement of Diabetes Australia,[35] and was also irrespective of whether or not the individual had diagnosis of impaired fasting glucose, or impaired glucose tolerance. No member of the preDM group was on medication. In the preDM group, 12 had shown high BGL during a visit different from when samples for this study were collected, while 19 showed high BGL in the visit where the sample for this study was collected, and three had established diagnosis of impaired glucose tolerance.

The DM+CVD group included individuals with established diagnosis of both DM and CVD. All members of this group were on medication, of which most were being treated with a combination of hypoglycaemic drug plus one or more of a hypolipidaemic agent, aspirin, anticoagulant and other cardiovascular medication.

Methodology

Age, blood pressure, CVD and/or DM diagnosis as well as smoking status were recorded for analysis. Participants were tested for three main biochemical risk profiles: cholesterol profiles including TC, HDL-cholesterol and TC:HDL ratio; macrovascular events profile including D-dimer, homocysteine and viscosity at low shear rate as markers of thrombosis, endothelial dysfunction and blood flow shear

Table 1. Mean±SD of variables for groups and intervals of levels of logistically important variables for quartiles.

Mean±SD of variables for groups		
	PreDM	**DM+CVD**
n	34	37
Female/Male	12/22	20/17
Age (years)	58±11	66±9
BGL (mmol/L)	5.6±0.9	7.2±3.0
SBP (mmHg)	127.13	141.18
GSH (mg/L)	0.57±0.24	0.65±0.20
MDA (nmol/mL)	0.35±0.24	0.34±0.17
MetHb (%)	0.73±0.44	0.81±0.48
HDL (mmol/L)	1.22±0.32	1.23±0.40
TC (mmol/L)	5.04±1.14	4.29±1.12
TC:HDL ratio	4.37±1.44	3.71±1.33
D-dimer (µg/L)	164±28	263±24
HCY (µmol/L)	10.03±2.66	10.34±3.11
V-low (mPas)	5.70±2.90	5.85±2.44

Interval of levels for quartiles				
	Q1	**Q2**	**Q3**	**Q4**
BGL (mmol/L)	≤5.10	5.11–5.98	5.99–6.89	≥6.90
SBP (mmHg	≤124	125–133	134–144	≥145
TC (mmol/L)	≤3.84	3.85–4.69	4.70–5.43	≥5.44
GSH (mg/L)	≤0.56*			≥0.57†

Q: quartile, BGL: blood glucose level, HCY: homocysteine, SBP: systolic blood pressure (supine), TC: total cholesterol, SD: standard deviation, *: GSH low, †: GSH normal.

rate/stress, respectively; and EOS status including GSH, MDA and metHb.

Cholesterol profiles were analysed using the Cholestech LDX method.[36] Cassette kits and quality control sera were obtained from Cholestech (supplied by Point of Care Diagnostics, Australia). Plasma D-dimer was determined by immunoturbidometry using the MiniQuant-1 instrument protocol (Biopool, Ireland).[37] Homocysteine was determined by fluorescence polarisation immunoassay (Axis-Shield) using the Abbott AxSYM immunochemical automated analyser protocol.[18] Whole blood viscosity was measured using a Silenus viscometer.[38] The EOS indices were measured by spectrophotometric techniques. Erythrocyte GSH was determined by the 5,5-dithiobis-2-nitrobenzoic acid (DTNB) reaction method.[39] Assay for MDA was based on the thiobarbituric acid reactive substances (TBARS) protocol, and metHB by the cyanmethaemoglobin method.[40,41]

Statistical analysis was performed using the SPSS package (version 14 for Windows). Binomial logistic regression was employed, being a gold standard for outcome prediction.[42] In the first step, four instances of regression analysis using forward likelihood ratio as a stepwise decision tool was performed. The explanatory variables included all the current screening parameters (i.e., age, BGL, cholesterol profile, gender, smoking and systolic blood pressure) and emerging indicators (EOS indices and markers of related cardiovascular events). In the second step, the coefficients or logistic equation obtained were used for the calculation, which in turn was transformed to probability (*P*).

Results

Table 1A shows the mean±SD of all test variables. In Table 1B the quartile divisions of the logistically important variables are shown. Values of BGL, BP, GSH and TC were transformed into four continuous graded categories based on the quartile intervals presented in Table 1B. Using the current screening factors (with diabetes status as a dichotomous variable), it was impossible to generate a logistic equation.

However, when using BGL as a continuous variable, logistic regression correctly identified members of the preDM and DM+CVD groups at 70.6% and 78.4% accuracy, respectively (Table 2). Statistically significant were BGL ($P<0.04$), systolic blood pressure ($P<0.02$) and TC:HDL ($P<0.05$). Age, gender and smoking were not retained.

Included are all emerging/tested biochemistry parameters, although GSH was ranked and categorised as normal and low based on the upper and lower 50% ranks, respectively. The study demonstrated 76.5% and 75.7% correctly identified membership of the preDM and DM+CVD groups, respectively. Statistically significant were BGL ($P<0.03$), BP ($P<0.02$), GSH ($P<0.04$) and TC ($P<0.02$) (Table 2).

Finally, when BGL, BP and TC were ranked and categorised into quartiles and, along with the categorised GSH, were included in a logistic regression analysis, 28/34 (82.4%) and 29/37 (78.4%) members were correctly identified in the preDM and DM+CVD groups, respectively. The 17.6% ($n=6$) incorrectly classified in the preDM group presented a probability of ≥0.51, while the 21.6% ($n=8$) incorrectly classified in the DM+CVD group presented a probability of ≤0.50 on the scale shown in Figure 2.

Table 2. Result of second instance of regression analysis using current risk assessment factors, substituting BGL* (formatted computer output)

		Group		% Correct
		PreDM	DM+CVD	
Group	PreDM	24	10	70.6
	DM+CVD	8	29	78.4
Overall percentage				74.5

BGL*: blood glucose level as continuous variable substituted for categorical (Yes) or (No) for established DM diagnosis.

The probability scale indicates the chance of membership of DM+CVD as the scale approaches 1.0 as an endpoint. For example, nine of the 34 preDM group members, assuming they were all unknown, have ≤0.1 (i.e., ≤10%) likelihood of being members of the DM+CVD group; and 10 of the 37 DM+CVD group members have 0.91–1.00 (i.e., near absolute) likelihood of being in this group.

When the logistic equation obtained from the final analysis was used in the formulation of a model chart, Table 3 was obtained. The basis of the risk chart model relies on the probabilities from the logistic equation. Logistic probabilities lie between 0 and 1. For example, if the probability was within the range 0.5–1, the individual was classified as DM+CVD.

Discussion

This study investigated three main risk profiles associated with the EOS pathway for the progression of diabetes and its cardiovascular complications, combined with some traditional risk factors as identified by the Framingham and NZGG screening models. The objective was to investigate the feasibility of a separate model additive, similar to but not altering the existing NZGG model. Therefore, cholesterol profile and other currently used factors (age, BP, diabetes, gender and smoking) were combined with the test indices of EOS and vascular events in logistic regression, in order to determine the combination of current and emerging factors that best identifies the probability of subclinical diabetic macrovascular complications in prediabetes.

First, using the current screening factors (i.e., DM and smoking as dichotomous variables; systolic blood pressure, TC:HDL ratio and age as continuous variables), it was impossible to generate a logistic equation. This was because diabetes status as a dichotomous variable is an exact statistical surrogate for the response (DM+CVD). The problem is that while DM status exactly differentiates the preDM group from the DM+CVD group, the likelihood of subclinical CVD in the former relative to established clinical CVD in the latter is not discriminated. So, the question remains: how do we screen for the prevalent subclinical macrovascular complications in prediabetes?

Diabetes status (as a dichotomous yes/no variable) was replaced with BGL as a continuous variable. This modification successfully identified 70.6% and 78.4% members of the preDM and DM+CVD groups, respectively

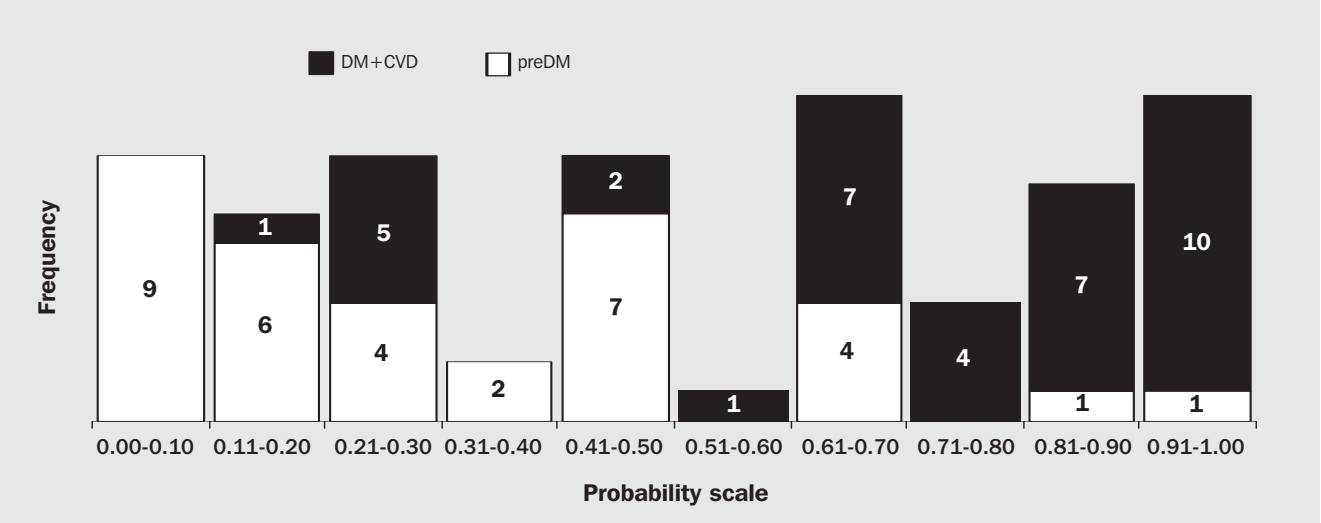

Fig. 2. Histographic presentation of the participants ($n=71$) on a probability scale, as obtained in the final logistic regression analysis.

(Table 2). This implies that 29.4% of the preDM group have been 'misclassified' to be members of DM+CVD group. When all emerging/tested biochemistry parameters were included, with erythrocyte GSH categorised as low/normal based on bottom/top halves of the ranked erythrocyte GSH levels, 76.5% correct identification of preDM group membership was seen, which is a 5.9% improvement in identification of individuals with prediabetes relative to those with diabetic macrovascular disease. More importantly, the improved identification also equals reduction in misclassification, which is indicative of subclinical macrovascular disease in prediabetes. The observed retention and significance of erythrocyte GSH provides a rationale to include EOS in the screening panel, especially for those non-smoking individuals with hyperglycaemia-induced GSH depletion. Furthermore, when BGL, BP and TC were ranked and categorised into quartiles, there was further improvement to 82.4% correct identification of the preDM group. This reduces misclassification to 17.6%.

There are two points to clarify. First, the improvements in correct identification of preDM group members, by the new combination of variables, represent the percentage of prediabetes individuals or undiagnosed DM that will be missed by the current screening models where BGL and oxidative stress are not taken into account. Specifically, including BGL in the model provides the basis for assessing the approximate 50% of undiagnosed type 2 DM in Australia as well as the 16% of Australians and over 40% of Americans who are estimated to have prediabetes.[6] This provides a rationale for an alternative risk model that includes BGL, erythrocyte GSH and TC to provide better risk indication of subclinical diabetic macrovascular disease for individuals with undiagnosed diabetes or prediabetes.

Second, the probabilities obtained from the logistic regression analysis (Fig. 2) indicates the likelihood of membership of the DM+CVD group. Logistic probabilities lie between 0 and 1. If the probability was within the range 0–0.5 the patient was classified as preDM but at low risk of CVD. If the model output probability lay between 0.5 and 1, the patient was classified as DM+CVD.

Part of the appeal of the current NZGG model is its simplicity. In order to keep using charts, there is a need to refit the LIPID prediction modelling exercise, including these new variables (A. Forbes, personal communication). Thus, the logistic equation model obtained in the final regression analysis was used to calculate the probabilities for all possible combinations of the new set of variables, and the result presented in a chart format (Table 3).

Using Table 3 and a set of BGL, BP, GSH and TC test results, an extrapolated probability ($P \leq 0.5$) for any unknown individual is expected to be 82.4% correct for prediabetes and low-risk CVD. However, the same model that identified 82.4% of prediabetes also identified 78.4% members of the DM+CVD group correctly. This implies that, using Table 3, an extrapolated probability for any unknown individual who is ≥0.51 is 78.4% likely to have diabetic macrovascular disease. In this study, six preDM group members, representing 17.6%, showed probabilities >0.5. These were considered as misclassified. However, from the clinical screening standpoint, these individuals have a 78.4% likelihood of subclinical macrovascular complication that requires intervention.

A critical review of the six misclassified cases showed that each individual had one (or no) current risk factor associated with coronary disease and thus did not qualify to be considered for intervention, but more than two risk factors in our proposed model to qualify for intervention. Thus, this model incorporating GSH and BGL provides an additional advantage of improved identification and targeted intervention against the likelihood of disease progression in prediabetes. Using two or more conventional/current risk factors only identifies persons with more severe CAD,[14–16] but not with subclinical disease. These findings are important as BGL and oxidative stress status, which underlie diabetic macrovascular pathogenesis, as part of a global risk equation will provide observation of more than two risk factors that will enable early intervention in persons with the subclinical disease.

It is noteworthy that the conventional factors are retained in the proposed model. The additional factors are hyperglycaemia and EOS indicated by GSH. It demonstrates that while smoking is not significant in the data, perhaps due to the small number of smokers, antioxidant status in relation to oxidative stress is significant; BGL as a continuous variable is required to adequately identify prediabetes and

undiagnosed DM in CAD screening; TC:HDL is used for screening in overt diabetes patients (TC is entered into the logistic model and may be more indicative of pathology in preDM individuals).

Reduced glutathione is as yet not a clinical diagnostic variable let alone a point-of-care test. This highlights the need to establish laboratory and point-of-care techniques for GSH. Furthermore, incorporating GSH in a screening model as an additional variable provides opportunity to fine tune treatment with regard to antioxidant supplementation. In fact, given the acceptance of oxidative stress involvement in macrovascular complications,[17,43] and speculated interaction between oxidative stress and atherothrombosis,[31,33,44] identifying and managing factors that are causally related to CVD,[45] including BGL and GSH in a screening model for early intervention in prediabetes is compelling.

It has been identified that more aggressive management of cholesterol and blood pressure is necessary in preventing diabetic macrovascular complications. The suggestion was based on the observation that opportunities for cardiovascular disease risk reduction are being missed, due to a significant proportion of individuals not meeting targets for both cholesterol and blood pressure.[46] In prediabetes, there is no routine monitoring of blood glucose, glycated haemoglobin, ischaemic heart disease or vascular complications of diabetes. Instead, a 75 g oral glucose tolerance test initially performed annually, with subsequent individualised testing frequency, as well as smoking cessation counselling where applicable, is the practice.[35] The present study provides a model that enables a better decision regarding the future heart disease risk. It also provides a basis to counsel non-smokers who may be experiencing oxidative stress on appropriate dietary requirements.

The study has some limitations. Medication is not a factor in the current screening models and was not included in the

Table 3. Chart produced from the logistic regression analysis for assessment of the probability of diabetic macrovascular disease.

GSH (mg/dL)	BGL (mmol/L)	BP (mmHg)	Total cholesterol (mmol/L)			
			≤3.84	3.85–4.69	4.70–5.43	≥5.44
≤0.56	5.10	≤124	0.35	0.19	0.09	0.04
		125–133	0.53	0.34	0.18	0.09
		134–144	0.71	0.52	0.33	0.18
		≥145	0.84	0.70	0.51	0.32
	5.11–5.98	≤124	0.55	0.35	0.19	0.10
		125–133	0.73	0.54	0.34	0.19
		134–144	0.85	0.72	0.53	0.33
		≥145	0.93	0.85	0.71	0.52
	5.99–6.89	≤124	0.74	0.56	0.36	0.20
		125–133	0.86	0.73	0.54	0.35
		134–144	0.93	0.85	0.72	0.53
		≥145	0.97	0.93	0.85	0.71
	≥6.90	≤124	0.87	0.74	0.56	0.36
		125–133	0.93	0.86	0.73	0.55
		134–144	0.97	0.93	0.86	0.73
		≥145	0.99	0.97	0.93	0.85
≥0.57	5.10	≤124	0.69	0.49	0.30	0.16
		125–133	0.83	0.68	0.48	0.29
		134–144	0.91	0.82	0.67	0.47
		≥145	0.96	0.91	0.81	0.66
	5.11–5.98	≤124	0.84	0.69	0.50	0.31
		125–133	0.92	0.83	0.68	0.49
		134–144	0.96	0.91	0.82	0.67
		≥145	0.98	0.96	0.91	0.82
	5.99–6.89	≤124	0.92	0.84	0.70	0.50
		125–133	0.96	0.92	0.83	0.69
		134–144	0.98	0.96	0.92	0.83
		≥145	0.99	0.98	0.96	0.91
	≥6.90	≤124	0.96	0.92	0.84	0.70
		125–133	0.98	0.96	0.92	0.84
		134–144	0.99	0.98	0.96	0.92
		≥145	1.00	0.99	0.98	0.96

statistical model. However, as all participants in the DM+CVD group were on medical therapy, including statins in most cases, the observation of lower levels of TC in the DM+CVD group compared to the preDM group (Table 1) is probably due to medical management. This gives an incorrect impression that the likelihood of progression to the DM+CVD group decreases as TC increases. It also demonstrates that prior to diagnosis those in the preDM group fare worse than those with an established diagnosis. In this particular study, medication will definitely be a statistical surrogate. This is because members of the prediabetes group are not on any medication, unlike those in the DM-CVD group.

In order to perform appropriate logistic regression to generate a working screening model, there needs to be baseline measurements of the required variables during the prediabetes phase. These would be followed by repeat measurements on those individuals who progress to DM-CVD co-morbidity. It would be more accurate, even without controlling for medication, when levels of the variables are taken first at baseline and then at the time of DM+CVD diagnosis.

One member of the prediabetes group had a transient ischaemic attack six months prior to screening. The participant was given no medication and was not diagnosed with CVD. It is presumed that the participant's GP considered the event as random. Another had heart murmur one year after the 2004 screening. The individual is still not on medication. According to the criteria of the study, these participants were included, and this limitation is acknowledged.

In the prediction of future diabetes macrovascular complications, the proposed set of biomarkers should provide independent information on risk beyond that available from the current models.[16] Importantly, the biomarkers should be part of the pathophysiological pathway that originates from hyperglycaemia. In this article, all the components of the proposed model have been illustrated in EOS as one valid pathway. Furthermore, no statistically significant gender difference was found. It is intended that a prospective longitudinal analysis study on established prediabetes cohorts be carried out in order to assess the use of these variables in the assessment of likelihood of diabetes macrovascular complications in prediabetes.

Conclusions

This study reports the feasibility of developing a new model incorporating a different combination of variables including BGL as a continuous variable, blood pressure, erythrocyte GSH and TC levels for assessing the likelihood of subclinical diabetic macrovascular complications in the prediabetes state. It shows a possible alternative risk assessment chart that can better assess the probability of diabetic macrovascular disease in individuals with no diagnosis of diabetes and CVD. It identified 17.6% of prediabetes individuals that do not qualify for CVD intervention by current screening models, but a 78.4% likelihood of subclinical diabetic macrovascular complication. It presents a stepping stone to formulate a global screening model that addresses early identification and intervention in subclinical CVD for the estimated 10% of Australians who have diagnosed or undiagnosed prediabetes, and the nearly 50% with undiagnosed type 2 DM.

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