

Comparative Study of a Two-year Disease Management Programme for Patients with Diabetes in a Primary Healthcare Setting

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Introduction

Diabetes mellitus (DM) is the sixth commonest cause of death in Singapore in 2001¹ and is also the leading cause of end-stage renal failure and blindness in adults.¹ The crude prevalence of diabetes among adults in Singapore in 1998 was estimated at 9.0%.² Diabetes is also commonly encountered at the primary healthcare level and accounts for 7.9% of total cases seen in the National Healthcare Group Polyclinics in 2002.³

Primary care physicians play an important role in providing care for patients with diabetes. However, the majority of patients in Singapore with diabetes do not appear to have their condition adequately controlled, with 53% of patients having HbA1c of more than 8%.⁴

Evidence from trials had shown that with good glycaemic control, the development of microvascular complications could be delayed or prevented.^{5,6} A new strategy is needed to improve the diabetes control in patients in the primary care setting. Barriers to improving glycaemic control may be overcome by a system of collaboration between primary care physicians and diabetic educators.⁷ This is even more important in a busy primary healthcare setting where the contact time between the patient and the physician is limited.

In October 2000, the Ministry of Health, Singapore, piloted the Comprehensive Chronic Care Programme (CCCCP)⁸ at Choa Chu Kang Polyclinic from 1 October 2000. The polyclinic is a primary healthcare centre with an average of 194,000 attendances in 2001.⁹ As typical of a busy polyclinic, each doctor can only spend an average of a few minutes with each patient.

The programme consists of a structured, comprehensive protocol for care of patients with DM, hypertension and hyperlipidaemia. This programme was characterised by the following features:

- (1) Team-based approach for care of patients
The team consists of family physician, care manager, podiatrist and dietician
- (2) Structured clerking notes
Clinical notes are structured with reminders given at regular intervals for the doctor. Prompts are also present to suggest referral for poor control of targets
- (3) Structured notes and programme for care managers
Care managers are specially trained nurses who provide customised support care and monitor the progress of patients. Health education is individualised for each patients
- (4) Default tracking
Defaulters are tracked by the care managers and recalled if appointments are missed

A formative study suggested an improvement in DM control for diabetic patients in the CCCC group achieving a 2-point decrease in

HbA1c after 6 months as opposed to no change for the non-CCCC group.¹⁰ There was also an increase in patients achieving optimal diabetic control from 9.5% to 36.5%.

This is a follow-up study over a 2-year period to evaluate if the improvement seen at 6 months can be maintained and the overall effectiveness of such a disease management programme versus standard care.

Materials and Methods

The doctors in Choa Chu Kang Polyclinic referred patients with diabetes, hypertension and hyperlipidaemia into CCCC from October 2000. There was a tendency to enrol patients with more severe and complicated disease. The patients were assessed by the care managers and were enrolled into the programme if they were agreeable, making it an opt-in system.

Patients on the programme were classified into 4 different disease categories according to their disease severity, co-morbidities and complications. The categories are:

- Category 1 (Cat 1): On diet control only
Category 2 (Cat 2): On oral medication and/or insulin
Category 3 (Cat 3): With co-morbidities (hypertension and/or hyperlipidaemia)
Category 4 (Cat 4): With complications arising from diabetes

The initial programme started out identifying patients in all categories. For the purposes of our study, we only evaluated Cat 3 and 4 diabetic patients to concentrate on the patients with more serious disease.

We identified all Cat 3 or 4 diabetic patients who were enrolled in CCCC from 2 October 2000 to 30 April 2001. There were 164 patients (69.9% Cat 3 and 30.1% Cat 4) in the CCCC group. At the end of 24 months, 12 (7.3%) were followed-up at tertiary centres, 16 (9.8%) defaulted treatment, 8 (4.9%) were followed-up at other primary care facilities, 2 (1.2%) opted out of CCCC while 1 (0.6%) died. Five (3.0%) patients had incomplete data at the 24-month follow-up and were excluded.

They were compared with 183 Cat 3 or 4 patients who were not enrolled in CCCC (control). The patients in the control group were chosen retrospectively and matched for age. The same group of doctors and nurses managed them over the same period as the CCCC group. However, they were not part of any structured programme. These patients had been left out of CCCC entirely during the study period.

The measured outcomes were weight, body mass index (BMI), systolic blood pressure, diastolic blood pressure, HbA1c and low-density lipoprotein (LDL) at 0, 6, 12, 18 and 24 months.

The doctors took the blood pressures manually during each consultation by a sphygmomanometer. The weight and BMI were

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TABLE I: CHARACTERISTICS OF CCCP AND CONTROL POPULATION

	CCCP ¹ (n = 164)	Control (n = 183)	p
% Male (n)	43.9% (72)	42.6% (78)	0.810
Mean age (y)	58.5 ± 10.1	59.8 ± 9.0	0.194
Minimum age (y)	36	36	-
Maximum age (y)	78	78	-
% Insulin Dependent (n)	17.1% (28)	4.9% (9)	<0.001
% Hypertension (n)	68.3% (112)	78.1% (143)	0.038
% Hyperlipidemia (n)	76.8% (126)	69.9% (128)	0.148
% CVA ² /TIA ³ (n)	4.3% (7)	3.8% (7)	0.834
% Ischaemic Heart Disease (n)	11.0% (18)	9.8% (18)	0.728
% Category 3 (n)	70.1% (115)	66.1% (121)	0.425
% Category 4 (n)	29.9% (49)	33.9% (62)	-

¹CCCP: Chronic Comprehensive Care Programme; ²CVA: cerebrovascular accident; ³TIA: transient ischaemic attack

either recorded by the doctors or the care managers. HBA1c was performed in-house at the polyclinic by the same laboratory over the study period.

Statistical package used was SPSS for Windows Release 11.5.0. Chi-square test was used to evaluate significance of proportion and one-way analysis of covariance (ANCOVA) was used to evaluate the change in HBA1c.

Results

The selected characteristics of both groups at entry are shown in Table I. The CCCP and control groups were comparable in terms of age, severity classification, and presence of co-morbidity of stroke, heart disease and hyperlipidemia.

There were a higher proportion of CCCP patients on insulin compared to the control group ($p < 0.001$). In the CCCP group, 68.3% of patients had hypertension compared to 78.1% in the control group ($p = 0.038$).

The baseline mean HbA1c in the CCCP group was higher compared to the control group (9.8 ± 2.1 versus 8.2 ± 1.5) (Table II). However, the mean HbA1c were similar at 12 months for CCCP (8.0 ± 1.4) and control (8.2 ± 1.2). HbA1c showed a decrease of -9.8% (95%CI 12.9~-6.1) in the CCCP group and -0.8% (CI 3.1%~-1.6%) in the control group at 6 months. The two groups continued to show significant decrease beyond 12 months, on follow-up at 18 months (-8.0% for CCCP versus -4.0% for control, $p = 0.030$) and 24 months (-8.6% for CCCP versus -4.5% for control, $p = 0.030$).

TABLE II: AVERAGE VALUES ($\pm$ SD) OF 6 KEY PARAMETERS OF CCCP AND CONTROL POPULATIONS OVER 24 MONTHS

	Weight (kg)	BMI ²	Systolic BP ³ (mmHg)	Diastolic BP (mmHg)	HbA1c (%)	LDL ⁴ (mmol/L)
0 month						
CCCP (n = 163)	65.1±11.8	26.0±4.3	136.1±17.8	81.1±8.6	9.8±2.1	3.9±1.2
Control (n = 183)	66.5±12.0	27.0±3.7	136.1±15.5	80.4±7.4	8.2±1.5	3.7±1.0
6 month						
CCCP (n = 142)	64.6±11.5	25.7±4.1	132.6±13.0	79.9±6.8	7.9±1.6	4.1±0.8
Control (n = 183)	70.0±16.5	29.4±5.4	131.4±12.1	78.7±7.7	8.3±1.6	3.7±0.8
12 month						
CCCP (n = 128)	64.9±12.7	26.0±4.6	135.0±15.9	78.8±7.4	8.0±1.4	3.6±0.9
Control (n = 183)	67.5±13.8	27.5±4.7	136.1±15.6	79.2±8.6	8.2±1.2	3.6±0.9
18 month						
CCCP (n = 130)	65.7±13.4	25.9±4.7	134.4±14.6	78.8±7.7	7.7±1.3	3.7±0.9
Control (n = 183)	69.4±11.2	28.8±3.6	138.5±15.3	80.0±8.2	8.0±1.2	3.7±0.9
24 month						
CCCP (n = 117)	64.2±11.2	25.0±4.9	134.6±11.1	77.7±7.5	7.6±1.1	3.5±0.8
Control (n = 183)	61.8±7.7	22.5±8.5	136.3±15.2	78.7±7.4	7.9±1.2	3.4±0.9

¹CCCP: Chronic Comprehensive Care Programme; ²BMI: body mass index;

³BP: blood pressure; ⁴LDL: low-density lipoprotein

TABLE III: ONE-WAY ANALYSIS OF COVARIANCE (ANCOVA) TEST FOR HBA1c

	Mean change (95%CI ¹)		p
	CCCP ²	Control	
6 months (n = 111)	-9.8% (-12.9 ~ -6.1)	-0.8% (-3.1 ~ 1.6)	<0.001
12 months (n = 104)	-6.2% (-9.7 ~ -2.8)	-3.2% (-5.8 ~ -0.6)	0.182
18 months (n = 107)	-8.0% (-10.7 ~ -5.2)	-4.0% (-6.1 ~ -1.9)	0.030
24 months (n = 95)	-8.6% (-11.5 ~ -5.6)	-4.5% (-6.6 ~ -2.3)	0.030

¹CI: confidence interval; ²CCCP: Chronic Comprehensive Care Programme

One-way ANCOVA was not significant for weight, BMI and LDL levels.

Discussion

It has been estimated that annual per capita healthcare expenditure in the United States in 1997 was 4-fold for those with diabetes compared to the general population.¹¹ Good diabetes control can reduce complications, improve quality of life for patients and ultimately reduce the economic burden on the country.

With a rapidly ageing population and prolonged life expectancy,¹² the prevalence of diabetes is expected to increase in Singapore over the next few years. A sedentary lifestyle and changes in dietary habits also contribute to the worsening problem.

Diabetes is a chronic condition where long-term lifestyle modifications are necessary for control of illness. Care of patients should consist of education, motivation of patients and support for patients. As a significant proportion of diabetic patients are followed-up in primary healthcare, it is important to provide structured care, regular HBA1c checks to assess control and screening for complications.

A team-based approach to managing diabetes is especially important at the primary care level due to the amount of time a doctor can spend with the patient. A disease management programme provides a systematic and comprehensive care for our chronic patients. A multi-faceted disease management programme for diabetes can result in significant improvement in diabetic care.¹³ A disease management programme can lead to significant reduction in healthcare costs and other measures of healthcare use.¹⁴

Patients enrolled on our programme can discuss management issues with our care managers during their regular follow-ups together with telephone assess. Our care managers also conduct workshops, lectures and organise support groups. This constitutes an important component of education to increase patients' motivation and provides them with necessary knowledge for self-care.

Glycated haemoglobin also provides useful information on health status and future medical charges for patients.¹⁵ The results from our study show that HBA1c levels for patients on CCCP decrease by a mean of 8.6% compared to 4.5% for the control group.

The mean blood pressure change for both groups was not significant. However, the mean blood pressures in both groups were already low to begin with.

The benefits to diabetic patients can be observed from the results of our study. A decrease in HBA1c levels will ultimately lead to lower complications from diabetes and improved quality of life for our patients.

The limitation of this study is that we were unable to demonstrate significant improvement in weight loss and change in LDL levels. The challenge for us in the future is to fine-tune our programme to facilitate weight loss and decrease LDL levels in our diabetic patients.

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Special Poster Presentation

Tissue Microarray Study for Classification of Breast Tumours

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Introduction

Breast cancer is one of the most common malignancies and a leading cause of death among women. The sporadic (non-inherited) breast cancer that constitutes more than 90% of all breast cancer is a complex and heterogeneous disease, at both the clinical and molecular levels. Genetic changes resulting in altered mRNA and protein levels, such as the activation or amplification of oncogenes or the loss of tumour suppressor genes, have been described in breast tumorigenesis. The clinical and pathological heterogeneity of breast cancer hinders selection of appropriate treatment for individual cases exclusively based on the histopathologic status, such as tumour grade, stage and type. Recently, breast tumours have been classified by their gene expression profiles at gene or protein levels, and the variation in gene expression patterns provide a distinctive molecular portrait of each tumour or closely related group of tumours. This novel tumour taxonomy elucidates the biological variance of tumours and provides better insight into the complex biological process involved in tumorigenesis. The validation of such a classification on formalin-fixed paraffin-embedded tumour archives linked to clinical information in a high-throughput fashion would have a major impact on clinical practice. In this study, we aimed to test the ability of tumour tissue microarrays to sub-classify breast cancers based on the immunohistochemical profilings of biomarkers. Subgroups with high malignant potential will also be assessed.

Materials and Methods

A tumour tissue array and a normal tissue array were constructed from 97 tumours and corresponding non-tumour tissues, using a tissue-arraying instrument. A tumour array was composed of 97 tumours and 5 normal tissues (as internal control) and a normal tissue array consisted of 97 matched normal tissues and 5 tumour tissues (as internal control). Of the 97 tumours, 11.3% had a histological grade 1, 39.2% a grade 2 and 49.5% a grade 3. Consecutive 4 µm-thick TMA sections were cut and placed on charged polylysine-coated slides for immunohistochemical analyses. A panel of 7 important biomarkers (ER, PR, c-erbB2, Cox-2, p53, VEGF and PDGF) was applied to representative sections of the tissue arrays. Standard indirect immunoperoxidase procedures were used for immunohistochemical staining. Briefly, tissue microarray sections were deparaffinised and treated with 3% hydrogen peroxide in phosphate-buffered saline to block endogenous peroxidase activity. For ER, PR, c-erbB2 and p53, the sections were treated with an antigen retrieval solution (10 mM citric acid monohydrate, pH 6.0), which was preheated at 95°C for 10 minutes. For Cox-2, VEGF and PDGF, the sections were subjected to heat-induced epitope retrieval in a microwave oven using the DAKO® Target Retrieval Solution (DAKO Corporation, Carpinteria, CA, USA), according to the manufacturer's instructions. Monoclonal antibodies against the protein biomarkers were used as primary antibodies. All the sections

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were incubated with the respective primary antibody for 1 hour at room temperature, followed by the HRP-labelled polymer for 30 minutes and DAB+ substrate-chromogen solution for 5 minutes (DAKO EnVision⁺ System, DAKO). All stained sections were counterstained with haematoxylin, dehydrated and mounted. The density and percentage of the stained tumour cells were evaluated for different biomarkers and expression levels were graded as negative, weak, moderate and strong. A tumour with moderate to strong staining was considered as positive. The tumours were classified using a monothetic (binary variables) clustering algorithm (S-plus 2000 software). Pearson's chi-square test with Yate's continuity correction was used for statistical analysis. A p value of <0.05 was considered statistically significant

Results

Based on the intensity and percentage of stained tumour cells, 47 of 95 cases were Cox-2 positive and 31 of 93 cases were p53 positive. Positive staining is found in 53 cases for ER, 54 cases for PR and 30 cases for c-erbB2. VEGF and PDGF were overexpressed in 55 of 89 cases and 58 of 90 cases, respectively. Using the monothetic clustering algorithm, 2 distinct groups of tumours are characterised by the oestrogen receptor (ER) status and tumour grade. Group I included tumours with ER negative, 75% of them with a grade 3; whereas group II consisted tumours with ER positive, 52% of them with a grade 2 ($p = 0.0026$). Four biomarkers, c-erbB2, Cox-2, p53 and VEGF, were significantly overexpressed in group I; with statistically significant difference. There were no significant differences for p53 ($p = 0.079$) and PDGF ($p = 0.497$) expression between the two groups. Each group of tumours was further subgrouped based on the

VEGF status, and 8 subsets of tumours were identified according to the expression status of c-erbB2 and p53. These 8 subsets were defined as ER-/VEGF+/c-erbB2+, ER-/VEGF+/c-erbB2-, ER-/VEGF-/p53+, ER-/VEGF-/p53-, ER+/VEGF+/p53+, ER+/VEGF+/p53-, ER+/VEGF-/p53+ and ER+/VEGF-/p53-. The correlations of these biomarkers were group dependent. The direct association of p53 with c-erbB2 was found in group I ($p = 0.048$). Co-expression of Cox-2 with VEGF was mostly found in subgroup ER-/VEGF+ rather than in subgroup ER+/VEGF+ ($p = 0.006$). c-erbB2 was significantly co-expressed with either Cox-2 or VEGF in subgroup ER-/VEGF+, not in subgroup ER+/VEGF+ ($p = 0.011$ and $p = 0.015$, respectively). The malignant potential of the ER-/VEGF+ subgroup was associated with the strong correlations of Cox-2 and c-erbB2 with VEGF.

Conclusion

Our results indicate that this molecular classification system, based on the statistical analysis of immunohistochemical profiling, is a useful approach for tumour grouping. The created subgroups may represent more homogeneous disease entities with definable genetic mechanism and may allow further study of specific genetically-controlled metabolic pathways. This approach may hold great promise in identifying biologically homogeneous subgroups in which molecular interactions can be easily addressed. The tissue microarray-based classification with limited protein biomarkers can sub-classify tumours into clinically and biologically relevant subgroups, and rationalise the application of different therapeutic strategies for different subgroups of breast.