REDESIGNING TREATMENT STRATEGIES IN TYPE 2 DIABETES BY TREATMENT INTENSIFICATION AND PATIENT EDUCATION

by

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ABSTRACT

Type 2 diabetes is a complex disease that is characterized by insufficient insulin production or utilization. Type 2 diabetes is associated with complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, atherosclerosis, peripheral artery disease and coronary heart disease. Three important risk factors for complications are hyperglycemia, hypertension and dyslipidemia.

Effective diabetes care involves self-management of the disease with proper nutrition, physical exercise and pharmacological agents that can control levels of glucose, cholesterol and blood pressure. With the rise in the prevalence of diabetes and often ineffective treatment intensification it is necessary to consider new treatment strategies. Patient centered approaches along with treatment intensification and diabetes education can be one such strategy to improve diabetes care. Diabetes education can be helpful as it helps in promoting healthy behaviors and appropriate diabetes self-management.

The objective of this study was to evaluate the effectiveness of providing patient education and intensifying treatment in patients with Type 2 diabetes and determine if there were significant changes observed in HbA1c, LDLc, blood pressure and adherence. This study specifically reported changes in patients at the 3 month follow up. The study was

a prospective, cluster randomized controlled trial. There were a total of 240 patients enrolled in the study: 175 were in the intervention group and 65 were in the control group. Treatment was intensified according to pre-approved protocols and diabetes education was provided to patients in the intervention group.

There was significant decrease in HbA1c and LDLc levels within the intervention group but the difference was not significant within the control group. There was no decrease in blood pressure within the intervention or the control group. HbA1c, systolic blood pressure and diastolic blood pressure was significantly different in between the groups at baseline but not during 3 month follow up. There was no statistically significant difference between the underlying distributions of the adherence scores of control at baseline or 3 month follow up.

The results from the 3 month follow up strongly indicated that treatment intensification along with patient education can be an effective way to treat diabetes. These results also emphasized the importance of a patient centered approach and diabetes education. The public health significance of this study is that it can be very helpful to optimize treatment strategies in diabetes while addressing behavioral and psychological needs of a patient. This can improve self-management of diabetes, which is one of the very important aspects of diabetes care.

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1.0 INTRODUCTION

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces (1). The insufficient insulin in the body causes hyperglycemia. Diabetes is characterized by symptoms such as frequent urination, excessive thirst, unexplained weight loss, extreme hunger, sudden vision changes, tingling or numbness in hands or feet, fatigue, very dry skin and wounds that are difficult to heal (2).

There are two main types of diabetes. Type 1 and Type 2. Type 1 diabetes was formerly called juvenile onset diabetes, usually develops in childhood or adolescence and is characterized by hyperglycemia due to an absolute deficiency of the insulin hormone produced by the pancreas (1). Type 2 diabetes usually develops during adulthood, however recently there has been an increase in incidence in children and adolescents (1). Type 2 diabetes is characterized by hyperglycemia caused by insulin resistance (1). This thesis focuses only on Type 2 diabetes.

1.1 EPIDEMIOLOGY

The World Health Organization (WHO) predicts that diabetes will be the seventh leading cause of death by 2030 (1). Diabetes has already been diagnosed in 347 million people all over the world. WHO also predicts a 50 percent increase in the number of deaths due to diabetes by 2030 (1). According to this report by WHO an estimated 3.4 million people died due to consequences of diabetes and more than 80% of the deaths occurred in low and middle income countries (1).

According to National Diabetes Statistics Report, 2014 by the Centers of Disease Control and Prevention (CDC), diabetes remained the 7th leading cause of death in the United States in 2010 (2) with Type 2 accounting for 95% of the cases. One in ten adults have diabetes in the United States (3). The prevalence of diabetes in the year 2012 in the United States was 9.3% and affected 29.1 million Americans. Out of 29.1 million people affected, 21 million were diagnosed and 8.1 million were undiagnosed. Approximately 11.6 million people with diabetes were over the age of 65 (3). Diabetes is slowly increasing in young adults affecting 208,000 Americans under age 20 (3). In 2012, 1.7 million new diabetes cases were reported of which 7.6% of non-Hispanic whites, 9.0% of Asian Americans, 12.8% of Hispanics, 13.2% of non-Hispanic blacks, 15.9% of American Indians and Alaskan Natives (3).

Total cost of diagnosed diabetes in the United States in 2012 was $245 billion of which $176 billion was spent on direct medical costs and $69 billion on reduced productivity (3). The cost of expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes (3). There has been a significant increase in the costs of diabetes from previous years, which indicates the high economic burden due to diabetes (3).

1.2 ETIOLOGY

In Type 2 diabetes, insulin secreted is insufficient or the insulin produced cannot be used by the human body. By definition, diabetes is a blood glucose level of greater than or equal to 126 milligrams per deciliter (mg/dL) after fasting overnight, or a non-fasting glucose level greater than or equal to 200 mg/dL along with symptoms of diabetes including a glucose level of greater

than or equal to 200 mg/dL on a 2-hour glucose tolerance test, or an HbA1c greater than or equal to 6.5% (4).

The cause of Type 2 diabetes is still remains unknown. Genetic susceptibility, autoimmune factors and environmental causes are strongly linked with diabetes. Obesity and physical inactivity are also strongly associated with development of Type 2 diabetes. Other possible causes of diabetes include insulin resistance, abnormal glucose production by the liver, the regulation of insulin and glucagon, metabolic syndrome and beta cell dysfunction (5).

1.3 RISK FACTORS

The risk factors for Type 2 diabetes are age, obesity, physical inactivity, having a parent or sibling with diabetes, family ancestry that is African American, Alaska Native, American Indian, Asian American, Hispanic/Latino, or Pacific Islander American. History of a live birth of more than 9 pounds, history of gestational diabetes, high blood pressure of 140/90 mmHg or above, being treated for hypertension, high-density lipoprotein (HDL) below 35 milligrams per deciliter (mg/dL), or a triglyceride level above 250 mg/dL, polycystic ovary syndrome (PCOS), an HbA1c level of 5.7 to 6.4 percent, a fasting plasma glucose test result of 100–125 mg/dL (impaired fasting glucose), 2-hour oral glucose tolerance test result of 140–199 mg/dL, impaired glucose tolerance, acanthosis nigricans, a condition associated with insulin resistance, characterized by a dark, velvety rash around the neck or armpits and history of CVD (5) are also considered as risk factors for Type 2 diabetes.

In addition to full blown Type 2 diabetes, pre-diabetes is a condition in which a person has a blood glucose level that is higher than normal, but not high enough to be diagnosed

diabetes (2). Individuals with pre-diabetes are at a higher risk for developing Type 2 diabetes and other serious health problems, including heart disease, and stroke (2). Without lifestyle changes, 15% to 30% of people with pre-diabetes will develop Type 2 diabetes within five years (2).

The risk factors of pre-diabetes are age especially above 45 years, being overweight or obese, a family history of diabetes, having an African American, Hispanic/Latino, American Indian, Asian American, or Pacific Islander racial or ethnic background, a history of gestational diabetes or having given birth to a baby weighing nine pounds or more and sedentary lifestyle (2). In 2012, 86 million Americans age 20 and older had pre-diabetes, which was greater than 79 million in 2010 (3).

1.4 COMPLICATIONS OF DIABETES

Diabetes has the potential to have deleterious impact on risk factors for complications such as hyperglycemia, hypoglycemia, hypertension and dyslipidemia. These risk factors can lead to an increased probability for myocardial infarction, stroke, blindness and eye problems, kidney disease, amputations and death due to cardiovascular complications (2).

Complications of diabetes can categorized into two types. Microvascular complications and microvascular complications.

1.4.1 Microvascular Complications

Microvascular complications in diabetes can cause significant mortality and morbidity. The susceptibility to complications depends on age, age at onset of the disease, environmental

factors, degree of glycemic control and disease duration (6). Some individuals are also genetically prone to develop these complications (6).

Diabetic retinopathy is one of the most common microvascular complication associated with diabetes. Approximately 10,000 diabetic retinopathy cases are reported every year in the United States alone (6). High levels of blood glucose, blood pressure and cholesterol, are the primary risk factors for retinopathy (7). In 2010, a total of 7,685,237 people were living with diabetic retinopathy (6) and about 20% of adults with diagnosed diabetes aged 45 years or older reported visual impairment compared with 15.7% of those aged 18-44 years (3).

The age-adjusted prevalence was 19% among women and 16.2% among men and the age-adjusted prevalence of adults with diagnosed diabetes who reported visual impairment was 20.7% for blacks, 17.1% for whites, and 15.6% for Hispanics in 2011(3). According to the UK Prospective Diabetes Study (UKPDS) development of retinopathy in Type 2 Diabetes was related to severity of hyperglycemia and presence of hypertension (8).

Diabetic nephropathy is the leading cause of renal failure in the United States (6). Small blood vessels in the kidneys are damaged due to diabetes making the kidneys less efficient, which leads to kidney failure. Diabetic nephropathy is more common in people with diabetes compared to people without diabetes (7). Diabetes is responsible for 30-40% of all end-stage renal disease (ESRD) cases in the United States (17). In between 1980 and 2008, the age-adjusted incidence of treatment for ESRD due to diabetes per 100,000 diabetic population varied by race-sex groups (3). It was greatest among black men and lowest among white women (3).

Micro albuminuria is defined as a condition in which albumin excretion is 30–299 mg/24 hours. Without any intervention and proper care, diabetic patients with micro albuminuria typically progress to proteinuria, which may lead to renal failure (6). In the UKPDS, the incidence of

micro albuminuria was 2% per year in patients with Type 2 diabetes, and the 10-year prevalence after diagnosis was 25 % (8).

There can be significant damage caused to the nerves due to high blood glucose and high blood pressure leading to many dysfunctions in the body. The most common affected area is the feet and this is called as peripheral neuropathy characterized by symptoms such as pain, tingling, and loss of sensation. The risk of developing diabetic neuropathy depends on the magnitude and duration of hyperglycemia which leads to nerve damage.

If neuropathy is not treated at the right time it can lead to infections and amputations. People with diabetes carry a risk of amputation that may be 25 times greater than that of people without diabetes (7). Diabetic neuropathy results in more than 80% of amputations due to foot ulceration and injury. Clinical and subclinical neuropathy has been estimated to occur in 10 to 100 percent of diabetic patients. Depending upon the diagnostic criteria and patient populations examined it is estimated 50 percent of patients with diabetes will eventually develop neuropathy (16). These complications may lead to mobility issues and the likelihood of developing neuropathy increases with age (3). Problems with mobility were observed more in women than in men (3). In 2011, among women, the age-adjusted prevalence was 62.6% for blacks, 56.6% for whites, and 50.9% for Hispanics and among men the age-adjusted prevalence was 51.9% for whites, 43.4% for blacks, and 43.1% for Hispanics (3).

1.4.2 Macrovascular Complications

The primary macrovascular complication associated with diabetes is atherosclerosis. This is characterized by narrowing of arterial walls throughout the body (6). Other than the formation of atheroma, there is a strong evidence of increase in hyper coagulabilty and platelet adhesion in

patients with Type 2 diabetes, which increases the risk of vascular occlusion (6). Atherosclerosis leads to the development of endothelial injury and inflammation due to accumulation of oxidized LDL particles in the endothelial wall of the arteries. This is called atheroma formation. Fibrinolysis can also be impaired in patients with diabetes, which increases risk for cardiovascular events.

In the Framingham Heart Study, the incidence of cardiovascular disease among diabetic men was twice that of non-diabetic men. Among diabetic women the incidence of cardiovascular disease was three times that of non-diabetic women (10). There was also a loss of female protective factors in premenopausal women due to onset of diabetes. (20)

Cardiovascular Disease (CVD) is the primary cause of death in patients with Type 2 diabetes. CVD also accounts for highest expenditures in healthcare among people with Type 2 diabetes (6). Diabetes increases the risk of developing CVD and is an independent risk factor for stroke and cerebrovascular disease. The risk of stroke is increased by 150-400% in people with Type 2 diabetes compared to people without Type 2 diabetes (6). Stroke related complications such as dementia and recurrence of stroke, and stroke related mortality is high among people with Type 2 diabetes. In 2011, among people with diabetes aged 35 years and older and with self-reported heart disease or stroke, 5.0 million reported having coronary heart disease, 3.7 million reported having other heart disease or heart condition, and 2.1 million reported having a stroke. The age-adjusted prevalence of self-reported heart disease or stroke was 35.5% among men and 31.5% among women (3). In 2011, the age-adjusted percentage of those reporting heart disease or stroke was 24.5% among Hispanics, 33.0% among blacks, and 33.9% among whites (3).

Peripheral artery disease (PAD) is a form of atherosclerosis, characterized by atherosclerotic occlusive disease of the lower extremities and is a marker for atherothrombotic disease in other vascular beds (19). PAD affects approximately 12 million people in the U.S totally. (19). PAD is considered as a major risk factor for lower-extremity amputation, especially in patients with diabetes (19). It has the potential to lead to major complications like myocardial infarction, stroke and death. Diabetes is one of the major risk factors of PAD along with smoking, age, hypertension and hyperlipidemia. The disease prevalence increases with age and 12% to 20% of Americans age 65 and older (4.5 to 7.6 million) have PAD. As the population ages, the prevalence could reach 9.6 to 16 million in those age 65 and older and 19 million overall by 2050 (21). One in every three people over the age of 50 with diabetes is likely to have PAD (21).

1.4.3 Risk Factors for Complications

Different complications in diabetes can be caused due to hyperglycemia, hypertension and dyslipidemia. Therefore these are considered among the primary risk factors for complications in diabetes.

1.4.3.1 Hyperglycemia

Hyperglycemia occurs when high amounts of glucose circulate in the plasma of the blood. It is associated with microvascular and macrovascular complications in diabetes (6). It can also cause cellular injury due to oxidative stress. Growth factors such as vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to play important roles in the development of diabetic retinopathy. Aldose reductase plays an important

role in development of diabetes complications. Osmotic stress from sorbitol accumulation has been postulated as one of the underlying mechanisms involved in the development of diabetic microvascular complications (9). In 2009, hyperglycemic crises caused 2,417 deaths, 19.8% lower than the 3,012 deaths in 1980 (3). In 2009, the hyperglycemic crises death rate was 42.6 per 100,000 diabetic population among black males, 19.5 among white males, 16.0 among black females, 11.7 among white females (3).

In the UKPDS study it was seen that chronic hyperglycemia, as measured by HbA1c, was one of the primary risk factors, which led to complications such as diabetic retinopathy, diabetic neuropathy, lower limb amputations and cardiovascular complications (8). HbA1c refers to glycated hemoglobin and is a longer term (2-3 month) measure of glycemic control. It develops when hemoglobin, a protein within red blood cells that carries oxygen throughout your body, joins with glucose in the blood, becoming 'glycated' (23). In the United Kingdom Prospective Diabetes Study (UKPDS) 5,102 patients with newly diagnosed Type 2 diabetes were recruited in 23 centers within the U.K. between 1977 and 1991.

The results established that retinopathy, nephropathy, and possibly neuropathy are reduced significantly by lowering blood glucose levels in Type 2 diabetes with intensive therapy, where a median HbA1c of 7.0% was achieved compared to median HbA1c of 7.9%. The overall microvascular complication rate was decreased by 25%. There was no decrease seen in the macrovascular complications (8).

In ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation,) 10,000 participants with Type 2 diabetes were randomized into four categories. They were intensive glucose lowering (including gliclazide MR) and additional “routine” BP lowering (perindopril/indapamide combination), standard glucose therapy and

routine BP lowering, intensive glucose lowering and placebo and standard glucose therapy and placebo. This trial involved 215 collaborating centers in 20 countries from Asia, Australia, Europe, and North America. By the end of follow-up, HbA1c in the intensive group had fallen to a mean of 6.5% compared with 7.3% in the standard group. HbA1c fell progressively in the intensive group, reaching 6.5% after 2–3 years duration of the trial. It was also seen that hyperglycemia was associated with microvascular events, (14% relative risk reduction, $p = 0.01$). A reduction in diabetic nephropathy was seen. There were no significant differences in the number of macrovascular events between the two groups during the trial (hazard ratio 0.94 [0.84–1.06] $P = 0.32$). (24).

In ACCORD (Action to Control Cardiovascular Risk in Diabetes), a total of 5,518 men and women with Type 2 diabetes were enrolled. All participants received simvastatin (20–40 mg/day) and were also randomly assigned to masked fenofibrate (160 or 54 mg/day, depending on renal function) or placebo. The primary outcome was the nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16).(25)

In Veterans Affairs Diabetes Trial (VADT), 1791 military veterans of mean age of 60.4 years who had Type 2 diabetes were randomized to receive either intensive or standard glucose control. The goal was to achieve absolute reduction of 1.5 percentage points in the glycated hemoglobin level in the intensive therapy group, as compared to standard-therapy group. After a median follow up was 5.6 years, median glycated hemoglobin levels were 8.4% in the standard-

therapy group and 6.9% in the intensive therapy group. There were no differences observed in between the two groups for microvascular complications. The rates of adverse events, such as hypoglycemia, were 17.6% in the standard therapy group and 24.1% in the intensive therapy group. (26)

1.4.3.2 Hypertension

Hypertension is one of the risk factors leading to complications in diabetes. According to the results obtained from Framingham Heart Study, hypertension has been identified as one of the major risk factor for the development of diabetes and its complications. Patients with hypertension are at a 2–3 times higher risk of developing diabetes than patients with normal blood pressure. Hypertension alone is, a powerful independent risk factor for cardiovascular morbidity and mortality (11).

The incidence of hypertension in patients with Type 2 diabetes is approximately two fold higher than in age-matched subjects without the disease (6). The prevalence is also higher in obese patients (11). There is a significant increase in hypertension with age (11). Both hypertension and diabetes have the potential to cause atherosclerosis (6). Therefore the coexistence can be more harmful to the body (11). The coexistence can also lead to thrombosis (11). Procoagulation can be caused in diabetic hypertensive patients due to enhanced platelet adhesion and aggregation of higher than normal levels of some coagulation factors (11). Hypertension causes ischemia in patients with diabetes and also speeds up the process of atherosclerosis of coronary arteries. (6) Hypertension is also a risk factor in causing End Stage Kidney Disease (ESRD) and accounts for 27% of all the cases in the US.

The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized control trial in which 12,866 men assessed to be at risk of coronary heart disease on the basis of higher levels of

serum cholesterol, diastolic blood pressure (BP), and cigarette use. Men were randomly assigned to special intervention or usual care. The special intervention (SI) group participated in an in depth sustained multifactor intervention program which basically aimed at lowering serum cholesterol and BP and at smoking cessation. The usual care group was offered no intervention. Cox models were used to assess the hazard ratios. In the MRFIT study the adjusted relative risk for developing ESRD was higher in hypertensive patients than in non-hypertensive patients. There were 885 deaths in special intervention group and 942 in the usual care group due to CHD (Hazard Ratio=0.94, 95% CI, 0.86–1.03). There were 1295 deaths special intervention group and 1332 deaths in usual care group due to CVD (Hazard Ratio=0.97, 95% 0.90–1.05) and there were 2713 deaths in special intervention group and 2735 deaths in usual care group from any cause (HR=0.99, 95% CI, 0.94–1.04). These were the numbers of deaths and hazard ratios after trial ended and an average of 27 years from randomization. (27)

In the ACCORD trial, systolic blood pressure in Type 2 diabetic patients at high risk for CVD was examined. A SBP of 120mmHg was set as the target. The study did not find any benefit in primary end point (nonfatal MI, nonfatal stroke, and cardiovascular death) comparing intensive blood pressure treatment (goal 120 mmHg, average blood pressure a goal achieved, 119/64 mmHg on 3.4 medications) with standard treatment (average blood pressure achieved 143/70 mmHg on medications). (25)

In the ADVANCE trial, the reduction in blood pressure showed some changes in the macrovascular events and risk of death due to cardiovascular causes in the intervention group. SBP was found to be significantly lower in individuals with intensive glucose control by the end of follow up (135.5 vs. 137.9 mmHg, average difference during follow up being 1.6 mmHg; $P < 0.001$). There were no significant differences in the number of macrovascular events between

the two groups (hazard ratio 0.94 [0.84–1.06]. Therefore, the differences were due to fewer micro vascular events (14% relative risk reduction, $P = 0.01$), essentially a reduction in diabetic nephropathy. (24)

1.4.3.3 Dyslipidemia

Dyslipidemia is one of the major risk factors leading to complications in diabetes. The parameters causing diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. There is an association seen in between hyperinsulinemia and low HDL levels (6). Insulin resistance together with dysfunction of the enzyme lipoprotein lipase (LPL) causes cardiovascular abnormalities. In diabetes the activity of the LPL is not to its maximum which causes high VLDL and low HDL levels. (6)

In the Framingham Heart Study, 13% of men and 24% of women with diabetes had increased total plasma cholesterol levels, compared with 14% of men and 21% of women without diabetes. The prevalence of high LDL cholesterol levels did not differ significantly. Prevalence of high plasma triglyceride levels in individuals with diabetes (19% in men and 17% in women) was significantly higher than in those without diabetes (9% of men and 8% of women). The prevalence of low HDL cholesterol level (defined as a value below the 10^{th}percentile for the US population) in those with diabetes was almost twice as high as the prevalence in non-diabetic individuals (21% versus 12% in men and 25% versus 10% in women, respectively) (28).

In UKPDS study, total cholesterol levels of those with diabetes mellitus and control individuals did not differ, but women with Type 2 diabetes had markedly higher LDL cholesterol levels than women who did not have diabetes. The plasma triglyceride levels of patients with

Type 2 diabetes mellitus were substantially increased, whereas HDL cholesterol levels were markedly reduced in both men and women with diabetes mellitus compared with the non-diabetic controls.(8)

Dyslipidemia is one of the major causes of coronary heart disease (CHD) (6). Lifestyle modifications involving diet and physical activity are advised for patients with dyslipidemia. But for the people whose cholesterol levels cannot be controlled by lifestyle modifications, statins are prescribed. Statins are given as the first line of treatment for dyslipidemia. There are some studies which provide evidence for reduction in cardiovascular events with the use of statins (29).

In the Scandinavian Simvastatin Survival Study (4S), 4444 subjects with previous myocardial infarction or angina pectoris and serum cholesterol of 5.5-8.0 mmol/L were randomized to simvastatin or placebo. The patients followed a lipid lowering diet and this was a double-blinded study. The subjects in the study were followed for 5.4 years. When a subgroup of 202 diabetic patients who participated in 4S was analyzed, results demonstrated that treatment for dyslipidemia reduced the risk of CHD. The magnitude of reduction was more in among those with diabetes (55%) than in those without (32%) (29) (30) (25).

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial included 9014 subjects followed up for 6.1 years in a double blind randomized study. The subjects were given pravastatin or a placebo. Subjects with a history of myocardial infarction or angina and total plasma cholesterol levels of 155-271 mg/dl were recruited into the study, 1077 subjects with dyslipidemia and diabetes and 940 patients with impaired fasting glucose (IFG) were followed. Subjects with diabetes were 61% more likely to develop CHD and patients with IFG were 23% more at risk to develop CHD compared to non-diabetics. (30)

1.5 TREATMENT OPTIONS FOR DIABETES

Treating diabetes can be very challenging as every individual is unique and the needs are different, however the basic goals of diabetic treatment are to control risk factors and prevent or delay diabetes complications. Different treatment options are listed below.

1.5.1 Self-management

Self-management is one of the very important aspects of diabetes care. Many concepts such as dealing with the symptoms of hyperglycemia and hypoglycemia, emotional issues such as depression, fear, anger, distress, and frustration, lifestyle changes such as healthy eating and exercise and medication adherence should also be addressed (18).

1.5.2 Nutrition

According to American Diabetes Association (ADA) nutrition therapy plays an important role in overall diabetes management. The ADA recommends that people with diabetes be actively engaged in self-management education and treatment planning with his or her health care providers. Collaborative development of an individualized eating plan is crucial. (22)

1.5.3 Physical Activity

Physical activity along with a healthy eating plan is very helpful in controlling diabetes and its complications. Even small amounts of less intense activity can lead to health benefits (22). Both

healthy eating and physical activity can improve glucose, blood pressure and lipid control (22). Therefore it can prevent or delay complications.

1.5.4 Medication

When high blood glucose cannot be controlled by exercise and diet then medications should be administered to control blood glucose levels. The most commonly prescribed medications for diabetes are listed in Table 1(14).

Treating hypertension in people with diabetes also involves lifestyle modification and medications. A healthy diet and physical exercise supports the treatment of hypertension (11). Most commonly prescribed drugs for hypertension are listed in Table 2.

Treating dyslipidemia in people with diabetes also involves lifestyle changes and medication. Most commonly prescribed drugs are listed in Table 3(45).

1.6 PATIENT CENTERED CARE

There are many pharmacological agents available in the market to treat diabetes, but the benefits and side effects of those agents vary from patient to patient. Patient preference, life expectancy, disease duration, comorbid conditions, socioeconomic status and cognitive status play a very important role in selecting the optimal treatment options (14). Therefore it is complex for physicians to decide on the optimal treatment strategy for patients. The American Diabetes Association and European Association for Study of Diabetes collaborated to investigate the evidence and developed recommendations for anti-hyperglycemic therapy in non-pregnant adults

with Type 2 diabetes (14). After the benefits and risks of glycemic control, efficacy and safety of anti-diabetic drugs and withdrawal of medication were examined; it clearly indicated the need for a patient centered approach to treat diabetes. (14)

Patient centered care is defined as "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions"(14). This approach gives importance to patient's needs and preferences. Individual specific treatment is the underlying principle of this approach. The patient is involved in decisions about diet, lifestyle and medications to a certain extent. Patient involvement in every step of treatment and decision-making is what makes it different from other approaches. In this process there is equal involvement of the physician and the patient in deciding the appropriate treatment, which can also contribute in increased adherence to the therapy (15). A patient centered approach involves effective self-management of diabetes and mutual exchange of information between the patient and the physician about different aspects of the disease and treatment (15).

A meta-analysis conducted by Norris et.al showed that diabetes education along with self-management interventions can improve glycemic control in patients with diabetes, although many factors can impede self-management of diabetes (31). The reasons may include, the patient may not be willing to use needles to take insulin, or the patient may lack the health literacy to read the instructions, or the patient may be uninformed about the dietary changes to be made to control diabetes (14). Access to quality diabetes care may also be a barrier to diabetes management. (14)

1.7 TREATMENT INTENSIFICATION

According to American Diabetes Association Standards of Care recommended goals for diabetes care are A1C less than 7%, blood pressure less than 140/80mmHg and LDLc levels less than 100mg/dl (22). Only one in 5 patients achieve this goal. There can be different reasons for this (14). Physicians may not prescribe the right medicine or may use insufficient doses of the medication or delay the initiation of the insulin therapy even though patients do have the access to care. This is referred to as clinical inertia (32). Clinical inertia is defined as failure to initiate a therapy when indicated, failure to titrate therapy until clinical goals are achieved or failure to perform a needed service (16). Evidence shows that 75% of clinical inertia can be attributed to a physician (32).

Treatment intensification is one of the ways to reach the clinical goals recommended by ADA standards of care where the patient will be given the appropriate dose of a medication moving towards the desired therapeutic goal or ultimately switched to insulin therapy if the oral glycemic agents are not showing the desired therapeutic effect (22). This is one of the strategies to manage clinical inertia, however there is little evidence demonstrating the most effective ways to overcome this barrier.

1.8 BEHAVIORAL ASPECTS OF DIABETES CARE

Adherence to medication is one of the very important aspects of diabetes care (23). Poor adherence impedes diabetes control (23). It is relatively easier for patients adhere to medications if there is an interaction among patients with healthcare providers. The behavioral theory

providing the foundation for this approach is called Self-determination theory. This theory implies that people are more likely adopt healthy behaviors when their basic physiological needs for autonomy, competence and relatedness are supported (32). Self-determination theory can be applied to diabetes patients as well. Patients with diabetes should take diabetes medications because they appreciate the importance of it rather than taking it because family or health care providers tell them to do so. The patients should have an understanding of the importance of a healthy lifestyle and taking medication on time. This helps the patient develop skills to manage their disease with more confidence, which, in turn, promotes healthy behavior and lifestyle.

A study was conducted by Geoffrey et.al (23) to apply the self-determination theory behavior to test medication adherence, quality of life and diabetes outcomes. Diabetes patients were identified from automated databases from 2003 to 2004 in an integrated health care delivery system. There were 2973 patients in the study. In 2005, patients responded to a mixed telephone and mail survey assessment, which was based on self-determination theory. In 2006 pharmacy claims data was used to predict adherence and patients HbA1c, glucose levels and non-HDL cholesterol were measured. Results indicated that application of self-determination theory in diabetic patients proved to be beneficial and helpful in diabetic self-management. There was positive association between application of self-determination theory and quality of life. Medication adherence correlated with glycemic control and non-HDL cholesterol.

1.9 SUMMARY OF THE LITERATURE REVIEW

Type 2 diabetes is a complex disease that is characterized by insufficient insulin production or inefficient use of insulin. The cause of the disease still remains unknown. Type 2 diabetes is

associated with complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, atherosclerosis, peripheral artery disease and coronary heart disease. The risk factors for complications are hyperglycemia, hypertension and dyslipidemia. Studies such as UKPDS (8), ACCORD (25), ADVANCE (24) and VADT (26) showed associations between hyperglycemia and diabetic complications. Framingham heart study (28), MRFIT (27), ADVANCE (24) and ACCORD (25) study established hypertension as one of the major risk factors leading to complications in diabetes. Studies such as LIPID (29) and 4S (30) established association between dyslipidemia and diabetic complications.

Effective diabetes care involves self-management of the disease with proper nutrition, physical exercise and pharmacological agents that can bring down the levels of glucose, cholesterol and blood pressure. With the rise in prevalence of diabetes and ineffective treatment strategies it is necessary to undertake to new treatment strategies. Patient centered approaches along with treatment intensification and diabetes education can be one such strategy to improve diabetes care. Diabetes education can be helpful as it helps in promoting healthy behaviors and self-management.

With a significant increase in the prevalence of diabetes, the incidence of complications related to diabetes also increases. According to the National Diabetes Statistics Report 2014, the number of people living with diabetes in the United States is expected to increase from 29.1 million to 48.3 million by 2050 which is alarming (3). The cost of disease increased from $147 billion in 1997 to $245 billion 2012(3). This clearly indicates the need for a different approach to manage diabetes and its burden (3).

2.0 METHODS

2.1 BACKGROUND

The goals to be reached according to the American Diabetes Association Standards of Care (22), are HbA1c less than 7%, blood pressure of 140/80mmHg, and LDLc levels less than 100mg/dl, however only one in five adult diabetes patients reach this goal (22). It is difficult to achieve these goals because the opportunities for timely intervention are often missed in a primary care setting. There are different reasons as to why this goal is not reached in 80% of the patients. It can be due to poor treatment outcomes, poor treatment adherence or clinical inertia. These are important issues that need to be addressed. The other important factors for successful diabetes outcomes include diabetes self-management education, patient-centered care, and adequate use of preventive services.

There is enough evidence that supports the fact that treating hyperglycemia and hypercholesterolemia and hypertension can reduce mortality and morbidity in people with diabetes, and this is possible if the goals set by ADA are achieved (22). Therefore it is necessary to systematically redesign the existing diabetes treatment strategies in the primary care setting by implementing certain changes that address issues including poor treatment outcomes, adherence and clinical inertia.

To address these issues, a cluster-randomized trial called REMEDIES 4D- REdesigning MEDication Intensification Effectiveness Study for Diabetes was conducted to evaluate the effectiveness of implementing REMEDIES 4D protocols on patient outcomes compared with usual diabetes care in primary care settings. This study used two approaches including patient centered care and treatment intensification delivered by certified diabetes educators. Intensifying the treatment and involvement of patients in the decision making process made this study unique.

2.2 SPECIFIC AIMS

The REMEDIES 4D study aimed to systematically redesign existing diabetes treatment approaches in a primary health care setting. The parent study aimed to

1a) To determine if those receiving care using the REMEDIES 4D protocols implemented by Diabetes Educator (DE) will have better clinical outcomes (e.g., HbA1c, blood pressure and LDLc)

1b) To determine if those who receive care using the REMEDIES 4D protocols implemented by DE will have improved treatment satisfaction, medication adherence, and patient activation;

This thesis is a sub study that will specifically:

1) Determine whether there were significant changes observed in HbA1c, LDLc, and blood pressure in the participants who received the REMEDIES 4D intervention compared with participants who did not at 3month follow-up.

2) Determine whether participants in the REMEDIES 4D intervention experienced improved treatment adherence compared with participants who did not at 3 months follow up.

2.3 HYPOTHESIS

Participants receiving the REMEDIES 4D intervention will have improved blood pressure, HbA1c, and LDL control, and treatment adherence compared with the patients who were not in the REMEDIES 4D intervention at 3 month follow-up.

2.4 STUDY DESIGN

REMEDIES 4D is a cluster randomized control trial. Certified Diabetes Educators (CDEs) intensified the treatment for hyperglycemia, hypercholesterolemia and hypertension according to specific protocols. The primary care practices from the University of Pittsburgh Medical Center (UPMC) were randomized to REMEDIES 4D protocols or usual diabetes care. Eight practices were randomized to intervention group and seven to the usual care group. The data from participants were obtained from medical records and questionnaires. Informed consent was obtained from all the patients and providers. The study was approved by University of Pittsburgh Institutional review board (IRB) under the number #REN11060090 /PRO08040023.

2.5 POPULATION

Practices: Primary care practices under UPMC (internal, general, family medicine) were considered. Practices had at least 50 people with diabetes. All practices had an electronic health record. The medical director who oversees these practices initially contacted 34 practices via

email. Interested physicians responded and met with principal investigator to discuss study. Interested physicians signed consent. Practices were randomly assigned by practice size by a flip of a coin to intervention or usual care. Fifteen practices involving 57 physicians and 2 physician assistants agreed to participate in the study. Two-thirds of practices had nursing staff and no practice had certified diabetes educators (CDE).

Patients: The eligibility criteria were patients 18 years of age and older, diagnosis of Type 2 diabetes at least one year prior to baseline, an HbA1c of ≥7%, LDLc of ≥ 100mg/dl or blood pressure ≥ 130/80mmHg. Eligible patients were identified through an alert, which was built into the electronic health record or posters in the office, posters or flyers in the office, or by direct referral by the physician. Eligibility was confirmed by phone screening. Eligible patients were seen in their primary care practice for the first visit where all the baseline data were collected.

2.6 SAMPLE SIZE

The initial desired sample size was 300 participants with 20 participants recruited from each of 20 practices. However 15 practices were recruited and a sample size of 240 was reached. Sample size estimations were based on differences in means in A1c of 1%, LDLc of 20mg/dl and systolic blood pressure (SBP) of 5mmHg between two groups at an Alpha=0.05 and with 80% power. Four parameters were used to determine the sample size, which were: No of clusters per group, the difference between group mean levels, intra cluster coefficient and standard deviation. An intra-cluster coefficient of 0.02 yielded a sample size of eight primary care practices per study group with 11 participants per practice. A dropout rate of 25% per practice was accounted

for in these calculations. (11/0.75=15: 15 x 8 x 2 =240). While recruitment was lower than expected, we were still able to detect significant differences, if our hypothesis was true, with a sample size of 240.

2.7 INTERVENTION

After participants were screened for eligibility, informed consent was obtained, blood pressure was taken and a foot exam was done by the CDE in the primary care practice. Medical history was reviewed. Eye and lab exams were ordered by CDE and treatment was intensified according to REMEDIES 4D protocols. Diabetes education was also provided to patients in the intervention group. The assessments were made at the baseline, three, six and twelve months. Primary outcomes were glycemic, blood pressure and lipid control and secondary outcomes was medication adherence.

Support groups were provided once in a month in the primary care practice or a nearby location to participants in control group.

2.8 GOALS OF REMEDIES 4D PROTOCOLS

Hyperglycemia:

a) Fasting plasma glucose(FPG) of ≤130mg/dl
b) A1C level <7%.

Dyslipidemia

LDL cholesterol is < 100 mg/dl or <70mg/dl if patient has overt CVD.

Hypertension

A blood pressure goal of <130/80 mm Hg.

American Diabetes Association Standards of care(22)

2.9 POTENTIAL CONFOUNDERS

Potential confounders in this study are age, gender, race, marital status, income, educational level, obesity, duration of diabetes, baseline levels of control for the primary outcomes, and depression.

2.10 STATISTICAL ANALYSIS

The primary outcome of this sub-study was lipid control, blood pressure control and glycemic control. The secondary outcome was medication adherence. Descriptive and univariate analysis were performed in this study. SAS 9.3 was used for analysis. Basic descriptive analysis such as means, medians, were used to describe continuous variables. Frequencies and percentages were used to describe categorical variables. A paired-t test was performed to measure the difference within the groups for LDLc, SBP and HbA1c between visit 1 and visit 2 for the intervention and control group. These variables were normally distributed. Visit number 1 represented the

baseline values and visit number 2 represented 3 month follow up data. A student's t test was performed to assess the difference between groups at baseline and the three month follow up.

Adherence was the secondary outcome of this sub-study. The Morisky scale was used to measure the adherence. The Morisky scale is a tool used to measure medication adherence. The MMAS 8 (Morisky Medication Adherence Scale) has 8 questions (41). The first seven questions are dichotomous response categories with yes or no answers. These questions assess unintentional non-adherence due to forgetfulness or due to travelling and intentional non adherence due to stopping medication without informing the doctor or due to some other hassles. Yes is scored as one and no is scored as zero. The last question has a five point response ranging from 0 to 4. A total score of 0 indicates high adherence, a score of 1 and 2 indicates medium adherence and a score of 3 and above indicates low adherence (42). A license was obtained to use this scale.

All the scores obtained from the Morisky scale (MMAS 8) (41) were totaled. This variable was not normally distributed. A Wilcoxon sum rank test was used to detect difference in between the intervention and control group and a Wilcoxon signed rank test was conducted to detect the difference within the intervention and control group.

3.0 RESULTS

Demographic and clinical characteristics of participants by intervention status at baseline are shown in Table 4. There were 240 patients involved in the study with 175 in the intervention group and 65 in the control group.

A paired t- test was conducted to compare the LDLc, HbA1c and blood pressure levels between the first visit and 3 month follow up. There was significant difference seen in LDLc in between the first visit (Mean=104.9 mg/dl, SD=40.0) and 3 month follow up (Mean=97.1, SD=31.8); p = 0.0007 within the intervention group but not within the control group. There was significant difference in HbA1c levels between the first visit (Mean=8.8, SD=1.8) and 3 month follow up (Mean=7.9, SD=1.5); p = 0.001 within the intervention group but not within the control group. There was no significant difference in SBP and DBP levels neither within the control group nor within the intervention group.

A student's t test was conducted to examine the differences in LDLc, HbA1c and blood pressure between the intervention and control group at baseline and three month follow up. There was a significant difference between the control and the intervention groups in HbA1c (p= 0.01), SBP (p=0.02) and DBP (p=0.01) at baseline but not at the 3rd month follow up.

Adherence was the secondary outcome of this sub-study. Since the Morisky total variable for diabetes, hypertension and dyslipidemia was not distributed normally a Wilcoxon sum rank test was conducted. The results suggested that there was no statistically significant difference between the underlying distributions of the adherence scores of protocol and the adherence scores of control ($z = -0.53$, $p = 0.59$) at baseline and there was no statistically significant difference between the underlying distributions of the adherence scores of protocol and the adherence scores of control ($z = -0.69$, $p = 0.48$) at 3 month follow up for diabetes medication.

There was no statistically significant difference between the underlying distributions of the adherence scores of protocol and the adherence scores of control ($z = -1.35$, $p = 0.17$) at baseline and there was no statistically significant difference between the underlying distributions of the adherence scores of protocol and the adherence scores of control ($z = -1.72$, $p = 0.08$) at 3 month follow up for hypertension medication.

There was no statistically significant difference between the underlying distributions of the adherence scores of protocol and the adherence scores of control ($z = 0.12$, $p = 0.89$) at baseline and there was no statistically significant difference between the underlying distributions of the adherence scores of protocol and the adherence scores of control ($z = -0.02$, $p = 0.98$) at 3 month follow up for dyslipidemia medication.

The results suggested that there was no statistically significant difference within control group and intervention group adherence scores for diabetes, hypertension and dyslipidemia.

4.0 DISCUSSION

4.1 SUMMARY OF FINDINGS

The present sub-study was conducted to test the implementation of the REMEDIES 4D study protocols on diabetic patients in a primary care setting. The results from the 3 month follow up strongly indicate that treatment intensification along with patient education can be an effective way to treat diabetes. These results also emphasize the importance of a patient centered approach and diabetes education. There was significant difference in HbA1c and LDLc levels within the intervention group but the difference was not significant within the control group. There was no difference in blood pressure within the intervention or the control group. HbA1c, systolic blood pressure and diastolic blood pressure were significantly different in between the groups at baseline but not during 3 month follow up. There was no statistically significant difference between the underlying distributions of the adherence scores of the intervention group and the adherence scores of the control group at baseline or 3 month follow up.

4.2 POSSIBLE EXPLANATION

Poor treatment outcomes may have been the result of insufficient doses of medication, clinical inertia (32) or due to lack of knowledge about the lifestyle changes that had to be made to achieve goals prescribed by American Diabetes Association (22) in diabetic populations. In this study the treatment was intensified according to the patient needs and pre-approved treatment protocols. Patients who had poor treatment outcomes were given higher doses of anti-diabetic medication or were encouraged to switch to insulin. Statins were administered in people with high LDLc levels. Diabetes education might have played a very important role in the change observed. Diabetes education may motivate patients to lead a healthy lifestyle and self-manage diabetes in a better manner, which may contribute to changes in LDLc and HbA1c levels.

The REMEDIES 4D study protocols may have contributed in improvement of health outcomes in patients through modification of treatment strategies in people with while addressing behavioral and psychosocial needs by providing patient education.

4.3 SIGNIFICANCE OF THE STUDY

Results from this sub-study indicate that a patient centered approach, treatment intensification and diabetes education play a very important role in diabetes care. The REMEDIES 4D study is the first of its kind to be implemented in a large number of practices with 15 primary care practices with 57 physicians and 2 physician assistants included. Other studies such as Medication Intensification in Diabetes in Rural Primary Care a Cluster-Randomized Effectiveness Trial (38) and Intensification of Insulin Therapy in Patients with Type 2 Diabetes

Mellitus an Algorithm for Basal-Bolus Therapy (39) were conducted with small sample sizes or in smaller practices.

There is a huge gap in literature that examines the role that can be played by nurses and pharmacists, independent of primary care physicians. Some studies facilitated by nurses to achieve reduction in HbA1c, blood pressure and LDLc resulted in improved in HbA1c, blood pressure, and LDLc levels (33, 34,35). Another study showed a 1.16% absolute reduction in HbA1c when pharmacists independently treated diabetic patients (36). In a study conducted by Davidson et al, the use of detailed protocols implemented by nurses or pharmacists proved to be effective (37). A meta-analysis covering all the studies in which pharmacists and nurses were allowed to make decisions about interventions without physicians approval showed a greater reduction in HbA1c when compared to other interventions (HbA1c mean decrease of 0.80% vs 0.32%, p=0.002) (38). Another study completely directed by pharmacists, with one year intervention, independent of primary care physicians, showed a greater reduction in heart disease (39).

Providing diabetes education to patients is not a novel concept as it has been done previously in some studies (43, 44) but the REMEDIES 4D study offered support to patients in primary care while providing behavioral and psychological support in a primary care setting. In this study nurses worked independently to intensify treatment that ultimately resulted in improved health outcomes. Physicians did approve the protocols but nurses intensified the treatment.

Factors such as clinical inertia and poor treatment outcomes are obstacles in diabetes care. There is a huge gap in research which addresses these issues. There is also a large gap in evidence supporting the effectiveness of patient centered care, diabetes education and treatment

intensification in larger populations or in multiple primary care practices limiting generalizability. The REMEDIES 4D study addresses these issues and the effectiveness of a patient centered approach along with treatment intensification and diabetes education.

4.4 STRENGTHS OF THE STUDY

The cluster randomized study design of REMEDIES 4D avoids the chance of contamination in the treatment group. The current treatment strategy for diabetes has been ineffective with only one in five people reaching the goal recommended by American Diabetes Association (23). The nature of the disease is complex and therefore difficult to treat. The current treatment modalities are not efficient and a new approach to treat the disease is needed. The REMEDIES 4D study implemented a holistic approach by providing patient centered care and support in primary health care. The team approach provided by nurses and physicians to achieve treatment goals where the behavioral needs of a patient are taken into consideration made this study unique. The approach used in REMEDIES 4D may provide a potential solution to address the increased prevalence of diabetes and its complications. This gives a new insight into diabetes care by using a patient centered approach. Issues such as medication adherence which is very important in diabetes care were also being addressed in this study.

In REMEDIES 4D, certified diabetes educators provided self-management education emphasizing the importance of taking medication and other lifestyle changes. During the three month follow up there was a significant reduction in HbA1c and LDLc levels. There was an absolute decrease of 10mg/dL in LDLc levels and 1.1% in HBA1c. This was likely due to better self-management of the disease and/or treatment intensification. Self-management of the disease

improves with diabetes education, which is grounded in self-determination theory. Treatment intensification may have played a very important role in the reduction.

4.5 LIMITATIONS

This study has certain limitations. A sample size of 300 with a patient number of 20 per practice was expected but a sample size of 240 was reached. The power was recalculated for the study and indicated even with the reduced sample size, statistically significant differences could be achieved, and however, there may have been some type 2 error in the study. Though eligible patients were identified through an alert, which was built into the electronic health record and posters in the office, physicians also recommended some patients into the study, which might have caused some selection bias. A follow-up period of 3 months of treatment intensification may not be enough to observe changes in blood pressure levels even though antihypertensive were administered. Though there were significant changes in HbA1c and LDLc levels in the intervention group it was observed that the subjects in control group had lower levels of HbA1c and LDLc levels when they enrolled into the study.

The Morisky scale was used to measure adherence in this study. MMAS-8 questions are designed to describe the medication taking behavior of patients but they seem not to be able to comprehensively assess the reasons or predictors of medication adherence (41). The possible reasons for non-adherence cannot be determined from MMAS-8 (41). This tool is helpful in identifying patients who have problems related to medication adherence but this tool is not good enough to report the improvement in adherence (41). This can be one of the limitations of this study.

Multivariate analyses was not performed in this study. Ideally mixed models should be used for this of cluster-randomized study. As only one variable can be used at a time, univariate models did not show a relationship between different factors due to inherent deficiencies. As only one variable can be changed at a time, univariate models are unable to show relationships between the variables. Different factors affecting the change in LDLc and HbA1c such as age, race, baseline values and diabetes duration could not be determined by univariate analysis.

4.6 FUTURE DIRECTION

There is a need for new diabetes treatment approaches as the prevalence of the disease is increasing day by day. The REMEDIES 4D study is one such approach to treat diabetes effectively and efficiently. This study can help researchers understand the factors that facilitate diabetes treatment and make it better for the patients. This study provides information on how nurses can intensify treatment independent of physicians in a primary care setting.

When the treatment was intensified for 3 months significant changes were seen in HbA1c and LDLc levels. This indicates that with further intensification of treatment and patient education better health outcomes can be seen. Blood pressure levels and adherence may also change significantly with longer periods of follow up.

The cost issues associated with this new approach should be focus of future studies. A detailed cost effective analysis that combines the cost and the health outcomes should be conducted to know the long-term impact of implementing REMEDIES 4D protocols on diabetic patients. Behavioral aspects such as patient activation and how it influences treatment intensification should also be analyzed in future studies. It is important to study how some

patients are motivated to change behaviors while some are not. Drugs used for treatment intensification can have certain side effects. Studies should be conducted to assess the change in quality of life after treatment intensification.

Research should also focus on the role that can be played patient centered medical homes (PCMH) as it emphasizes on patient centeredness in primary care (46). The importance and effectiveness of using inter professional practice in health care should be also be studied. Future studies should also assess the effectiveness of integrating patient centered care, treatment intensification and patient education in other chronic diseases.

4.7 PUBLIC HEALTH SIGNIFICANCE

With the increase in prevalence of diabetes it is important to integrate a patient centered approach, diabetes education and treatment intensification. Engaging nurses and pharmacists to intensify treatment in patients with Type 2 diabetes can be promising as they can help overcome barriers such as clinical inertia. This can be very helpful to optimize treatment strategies in diabetic patients. Addressing patient needs that are behavioral and psychological can improve self-management of diabetes, which is one of the very important aspects of diabetes care.

The involvement of nurses and pharmacists in diabetes can give a new dimension to diabetes care and we can reach out to treat more number of people with diabetes and help patients self-manage the disease in a better way.

APPENDIX: FIGURES AND TABLES

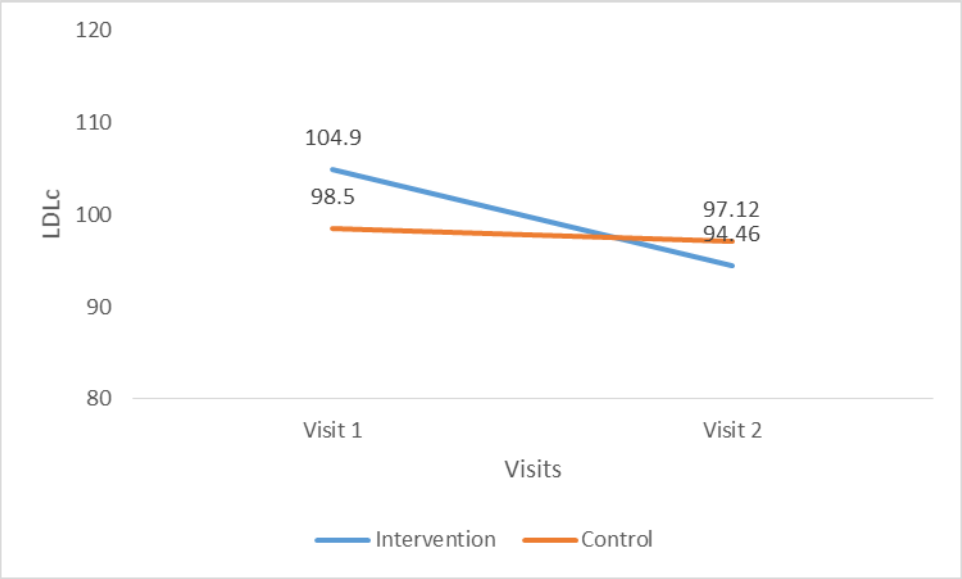

Figure 1. Change in LDLc levels from baseline to 3 month follow up

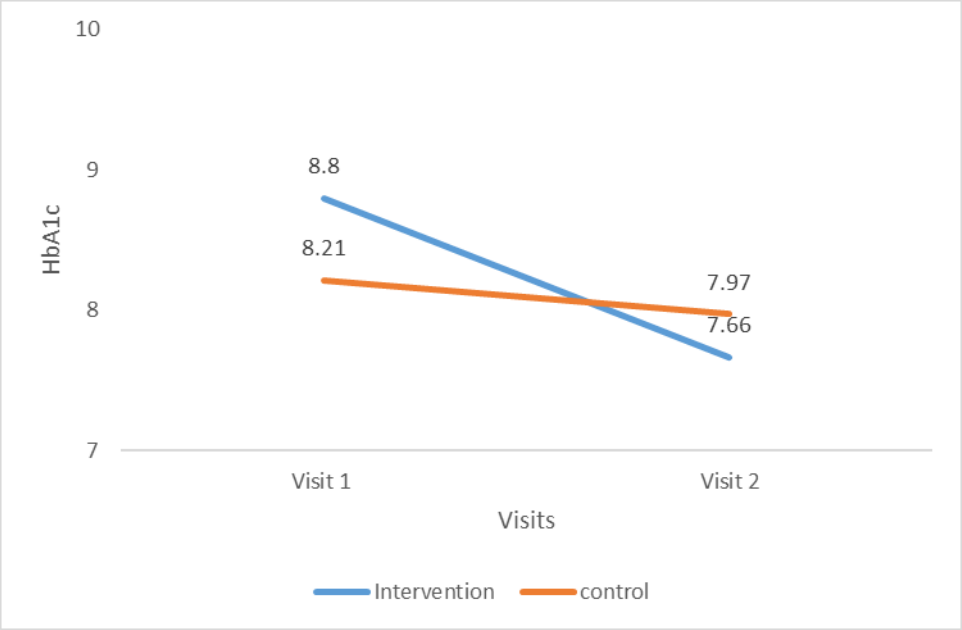

Figure 2: Change in HbA1c levels from baseline to 3 month follow up

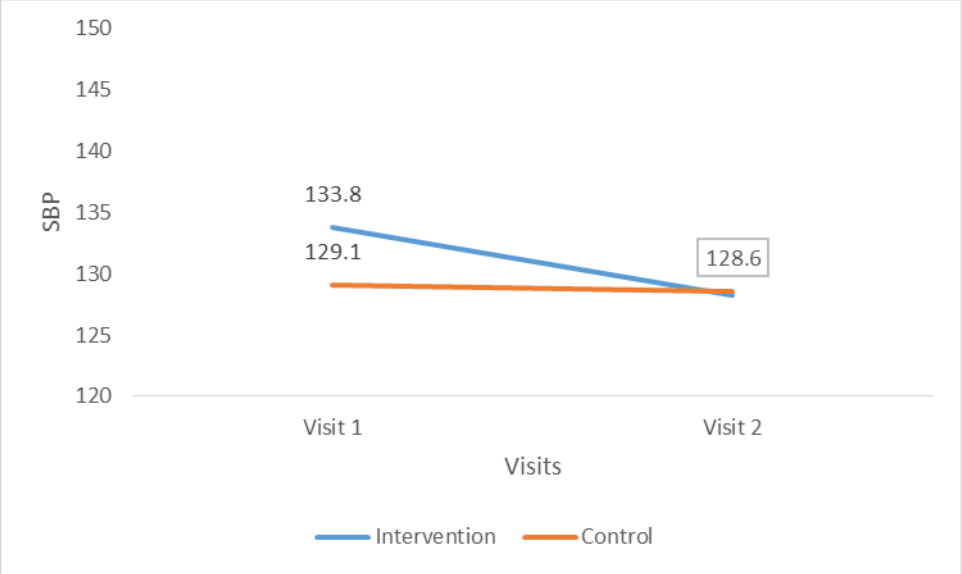

Figure 3: Change in SBP levels from baseline to 3 month follow up

Table 1. Drugs used in the treatment of Diabetes

Class of Drug	Generic Name
Biguanides	Metformin, Phenformin, Buformin
Sulfonyl ureas	Carbutamide,Acetohexamide,Chlorpropamide,Tolbutamide Glipizide,Gliclazide,Glibenclamide, Glyburide,Glibornuride,Gliquidone,Glisoxepide,,Glyclopyramide
Thiazolidinedione	Pioglitazone , Rosaglitazone
DPP-4 Inhibitors	Sitagliptin , Saxagliptin, Linagliptin
Alpha-glucosidase Inhibitors	Acarbose ,Miglitol
Bile Acid Sequestrants	Colesevelam
Combination Pills	Pioglitazone & metformin, Glyburide & metformin , Glipizide & metformin , Sitagliptin & metformin , Saxagliptin & metformin, Repaglinide & metformin , Pioglitazone & glimepiride

Table 2: Drugs used in treatment of Hypertension

Class of Drug	Example
ACE inhibitors	enalapril, lisinopril, perindopril.
Angiotensin II receptor blockers:	losartan, valsartan.
Calcium channel blockers:	diltiazem, nifedipine and amlodipine.
Diuretics:	amiloride, frusemide, indapamide
Beta-blockers:	atenolol, metoprolol, propanolol.
Alpha-blockers:	doxazosin, prazosin.
Centrally acting antihypertensive drugs:	methyldopa and clonidine
Vasodilators	hydralazine.

Table 3: Drugs used in treating Dyslipidemia

Class of Drug	Generic Name
Bile-acid sequestrants	Cholestyramine , Cholestipol
HMG-CoAreductase inhibitors or statins	Atorvastatin,Fluvastatin,Lovastatin Pravastatin,Rosuvastatin, Simvastatin
Fibric acid analogs	Clofibrate , Gemfibroxzil

Table 4: Demographic and clinical characteristics of participants in intervention and control group at baseline

		Intervention			Control		
Variables	**N**	**Mean %**	**Standard Deviation**	**N**	**Mean %**	**Standard Deviation**	**P- Value**
Age (years)	170	60.5	10.2	63	61.8	11.0	0.38
Diabetes Duration(Years)	170	12.2	8.6	63	10.7	7.3	0.17
Gender							0.49
Male	87	49.7		35	54.6		
Female	88	50.2		29	45.3		
Race							0.16
White	134	78.8		59		93.6	
Black	28	16.4		4		6.3	
Others	8	4.7					
Schooling							0.42
High School	64	36.6		21	32.3		
College	106	61.5		42	64.6		
Missing	5	2.9		2	3.1		
Employment							0.69
Employed	76	43.4		27	41.5		
Unemployed	41	23.4		13	20.0		
Retired	49	28.0		20	30.8		
Other	4	1.7		2	3.1		
Missing	5	3.4		3	4.6		
HbA1c (%)	175	8.8	1.7	62	8.2	1.3	0.01
SBP(mmHg)	175	129.0	14.5	62	133.7	13.7	0.02
DBP(mmHg)	175	76.7	7.8	62	79.9	9.1	0.01
LDLc(mg/dl)	172	104.9	40.0	58	98.5	37.3	0.27
Microvascular Complications(yes)	76	43.4		29	44.6		0.44
Microvascular Complications(yes)	100	57.1		41	63.1		0.88

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