FACTORS ASSOCIATED WITH NONACHIEVEMENT OF LOW DENSITY LIPOPROTEIN CHOLESTEROL TARGET AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABBREVIATIONS

ACS   Acute Coronory Syndrome

CHD   Coronory Heart Disease

DBP   Diastolic Blood Pressure

DM   Diabetes Mellitus

HDL   High Density Lipoprotein

HUSM   Hospital Universiti Sains Malaysia

KRK   Klinik Rawatan Keluarga

LDL-C   Low Density Lipoprotein Cholesterol

MCQ   Medication Compliance Questionnaire

NCEP-ATP   National Cholesterol Education Program Adult Treatment Panel

SBP   Systolic Blood Pressure

TG   Triglyceride

WHO   World Health Organisation

ABSTRACT

English Version

Tittle: Factors associated with nonachievement of LDL-C target among patients with Type 2 Diabetes Mellitus.

Introduction: Dyslipidaemia is a risk factor for cardiovascular disease and Type 2 Diabetes Mellitus is a cardiovascular risk equivalent. Low density lipoprotein cholesterol (LDL-C) is the primary target in the management of dyslipidaemia and achievement of LDL-C target according to National Cholesterol Education Programme (NCEP-ATP III) is crucial.

Statins are potents drug to reduce cholesterol especially the LDL-C,   however the effectiveness is limited by the poor adherence.

Objectives: To determine proportion of patients achieve LDL-C target and factors associated with nonachievers and the adherence to statin therapy among patients with T2DM.

Methodology: A cross sectional study involving 234 patients aged 18 years old and above who had comorbid Type 2 Diabetes Mellitus and Dyslipidaemia. Systematic Random Sampling with replacement method was applied to select participants who attended KRK, HUSM from January 2013 to May 2013. Both self-administered and interviewered administered questionnaires were used to obtain the socio demographic characteristics, clinical characteristics and compliance questionnaire. The data was analysed for descriptive statistic and multiple logistic regression.

Result: The percentage of LDL-C target achievement was 37.6%. The percentage of patients adhered to statin therapy was 98.3% and 20.5% of patients adhered fully. There was no significant relation between LDL-C achievement and adherence. Sociodemographic data(such as age, marital status, gender, education level and household income) and clinical data (such as smoking status, number of prescribed medications, BMI, SBP, duration on statin therapy and type of statin taken) were not associated with achievement of LDL-C target. HbA1c is the only significant factor that associated with LDL-C target achievement.

Conclusion: Achievement of LDL-C target among T2DM patients attended KRK,HUSM was still low. Majority patients were adhered to statin therapy however the relation between adherence and LDL-C achievement was not significant. HbA1c was the only significant factor associated to nonachievement of LDL-C target. Patients with poorly control glycaemic control should more holistically manage including achieving their LDL-C target.

Malay Version

Tajuk: Faktor-faktor yang mempengaruhi bukan pencapai dan kepatuhan terhadap ubat kolesterol jenis statin di kalangan pesakit Kencing Manis Jenis 2.

Pengenalan: Dyslipidaemia adalah faktor risiko bagi penyakit kardiovaskular dan penyakit Kencing Manis jenis 2 adalah risiko kardiovaskular yang setara. Kolesterol lipoprotein ketumpatan rendah adalah sasaran utama dalam pengurusan dyslipidaemia dan pencapaiannya mengikut *National Cholesterol Education Programme* (*NCEP-ATP III*) adalah penting. *Statin* adalah ubat antikolesterol yang berkesan untuk mengurangkan kolesterol terutamanya kolesterol lipoprotein ketumpatan rendah. Walau bagaimanapun keberkesanannya adalah terhad disebabkan oleh ketidakpatuhan terhadap ubat antikolesterol.

Objektif: Untuk menentukan tahap pencapaian sasaran koleterol lipoprotein ketumpatan rendah, faktor-faktor yang mempengaruhi bukan pencapai dan peratus kadar pematuhan terhadap ubat kolesterol jenis statin.

Metodologi: Ini adalah kajian rentas yang melibatkan seramai 324 pesakit berumur 18 tahun dan ke atas yang menghidapi penyakit Kencing Manis Jenis 2. Pemilihan sampel secara Sistematik Rambang telah dilakukan untuk memilih peserta yang datang ke KRK, HUSM dari Januari 2013 hingga Mei 2013. Borang soal selidik telah digunakan untuk mendapatkan ciri-ciri sosio demografi, ciri-ciri klinikal dan soal selidik pematuhan terhadap ubat. Data yang diperolehi telah dianalisis menggunakan statistik deskriptif dan regresi logistik berganda.

Keputusan: Peratusan pencapaian sasaran kolesterol lipoprotein ketumpatan rendah adalah 37.6%. Peratus pematuhan kepada ubat kolesterol jenis statin adalah 98.3% dan 20.5% pesakit telah patuh sepenuhnya. Tiada hubungan yang signifikan antara tahap pencapaian kolesterol lipoprotein ketumpatan rendah dan pematuhan terhadap ubat kolesterol jenis statin. Data sosiodemografi (seperti umur, status perkahwinan, jantina, tahap pendidikan dan pendapatan isi rumah) dan data klinikal (seperti status merokok, jumlah ubat-ubatan diambil, jisim index badan, tekanan darah sistolik, tempoh menggunakan ubat kolesterol jenis statin dan jenis statin yang diambil) tidak mempunyai kaitan dengan tahap pencapaian sasaran kolesterol lipoprotein ketumpatan rendah. HbA1c merupakan satu-satunya faktor yang ditemui mempunyai kaitan dengan tahap pencapaian lipoprotein ketumpatan rendah.

Kesimpulan: Pencapaian sasaran kolesterol lipoprotein ketumpatan rendah di kalangan pesakit Kencing Manis Jenis 2 di KRK, HUSM adalah masih rendah. Majoriti pesakit telah patuh terhadap pengambilan ubat kolesterol jenis statin. HbA1c adalah satu-satunya faktor signifikasi yang mempunyai perkaitan dengan tahap pencapaian kolesterol lipoprotein ketumpatan rendah. Pesakit yang mempunyai kawalan gula yang lemah perlu dirawat secara holistik termasuk memastikan target LDL-C juga dicapai.

CHAPTER 1

INTRODUCTION

1.1 Dyslipidaemia and Cardiovascular disease

Cardiovascular disease include coronory heart disease, cerebrovascular disease and peripheral arterial disease. Coronory heart disease is a spectrum of stable angina, ischaemic heart disease and myocardial infarction. According to Ministry of Health Malaysia, cardiovascular disease was the leading cause of death in 2009 for both men and women. In 2008, World Health Organization reported that cardiovascular disease is the top leading cause of death in the world among countries with average and high incomes which accounted about 13% to 16% of death. National Cardiovascular Disease – Acute Coronory Syndrome Registry (NCVD-ACS 2006-2008) reported that there is a high prevalence of established cardiovascular risk factor among patients with ACS which is rated at 31% to 35% in which patients had history of dyslipidaemia and in overall, 55.9% had abnormal cholesterol level(1).

Dyslipidaemia is a major risk factor for cardiovascular disease(2). Many epidemiologic studies have shown that dyslipidaemia is a strong predictor of the likelihood that an individual will developed cardiovascular disease. High LDL and low HDL has been demonstrated as risk factors which are causally linked to cardiovascular disease(2).

The Strong Heart Study assessed the cardiovascular disease risk factors in diabetic individuals. In this large cohort study, it was found that LDL cholesterol was a strong independent predictor of coronory heart disease and hazard ratio indicates that a 10mg/dL(0.6mmol/l) increase in LDL choleserol levels would lead to a 12% increase in cardiovascular disease(3). It is crucial to manage dyslipidaemia accordingly and pharmacological treatment should be initiated early if indicated. To achieve the target of controlled blood cholesterol level is not only done through drug therapy but also simultanously with the therapeutic changes of life style. A 12 years follow up study in the Russian Lipid Research Clinics observed a contradictory finding regarding association of risk of coronory heart disease and cholesterol level(4). Men with very low LDL-C had increased in coronory heart disease mortality and was described as a J-shaped curve. CHD death rate in men Russian patients with LDL-C less than 2.9mmol/l was slightly higher than patients with LDL-C between 2.9mmol/l to 3.4mmol/l resulting a J-shaped curve. However, they concluded that the J-shaped   relationship between LDL and CHD mortality was associated with lifestyle characteristic such as low educational achievement, high alcohol consumption, higher history of current smoking and lower mean BMI.

1.2 Dyslipidaemia and Diabetis Mellitus

Type 2 Diabetes Mellitus had more significant impact to the development of multiple microvascular and macrovascular complications   including coronary heart disease. Major clinical trials such as Multiple Risk Factor Intervention (MRFIT), The Prospective Cardiovascular Munster Study (PROCAM) and The Framingham Heart Study had shown relationship between Diabetes Mellitus and Coronory Heart Disease mortality(5-7).

National Health Morbidity Survey in 2011 found that 35.1% of adult aged 18 years old and above had hypercholesterolaemia and 26.6% were previously undiagnosed with hypercholesterolaemia(8).

Dyslipidaemia and Diabetes Mellitus are major predictors for cardiovascular disease as both clinical condition have an effect towards macrovascular disease and formation of artherogenesis (9). Individual with both clinical conditions are considered to be at a higher risk in developing cardiovascular disease and treating to target is really important to prevent further morbidity and mortality resulting from cardiovascular events.

The recognised features of LDL-C that predispose it becoming atherogenic and tending to promote the formation of fatty plaques in the arteries are small dense LDL-C and excessive postprandial lipemia(10). Small dense LDL-C particles easily penetrate the vascular endothelium and get deposited in the walls of the vessels(11). The percentage of individuals possessing small and dense LDL-C is higher by at least 2 folds in T2DM(11). Among patients with established cardiovascular disease or cardiovascular risk equavalent, pharmacotherapy should begin with adjuvant to therapeutic lifestlye modification including exercise and dietery intervention. LDL –C is the primary target for therapy and is dependant upon an individual's global cardiovascular risk.

1.3 Low Density Lipoprotein Cholesterol

Low density lipoprotein (LDL) is one of the five major groups of lipoproteins and the cholesterol which is bind to it is known as LDL cholesterol or is also well known as a bad cholesterol. The five major lipoproteins including chylomicrons, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein and high density lipoprotein varies in the term of size from largest to smallest. These lipoproteins have a function for transporting lipids like cholesterol and tryglycerides within the water based blood stream. LDL particles are very similar in size to the normal gaps in the endithelium. LDL particles can transport cholesterol into the arterial wall and be retained as arterial proteoglycans which attract macrophages that engulf the LDL particles and start the formation of plaques. These condition increased the risk of atherosclerosis. The atherogenicity of LDL cholesterol is well established and proven in many studies. Most of the major clinical trials have shown a direct relationship between level of LDL cholesterol and the risk of coronory heart disease either in a previously healthy population or in patients with the related diseases such as hypertension and diabetes mellitus. National Cholesterol Education Programme – Adult Treatment Plan I to III (NCEP-ATP III) has established LDL cholesterol as a primary target of therapeutic interaction because LDL cholesterol plays a major role in initiating the development of atherosclerotic plaque. Meta analysis have shown that reducing total cholesterol by 1mmol/l significantly reduces mortality due to coronory heart disease(12).

Justification of research

This research is conducted to determine primary lipid target achievement which is low density lipoprotein cholesterol and the adherence to statin therapy in patients with comorbid Type 2 Diabetes Mellitus and Dyslipidaemia. National Cholesterol Education Programme – Adult Treatment Plan I to III (NCEP-ATP I -III) has established LDL cholesterol as a primary target of therapeutic interaction because LDL cholesterol plays a major role in initiating the development of atherosclerotic plaque. It is crucial to achieve the target of LDL-C according to the recommended level as it prevent further risk of cardiovascular event. This study evaluated the current performance of LDL-C achievement in patients with Type 2 Diabetes Mellitus and reflected the management of dyslipidaemia of Type 2 Diabetes Mellitus. The adherence to lipid lowering therapy particularly statin group which was stated as the most potent antilipid in reducing LDL-C level is also important. Being aware of the factors associated with LDL-C achievement, can assist us in recognising patients which have tendency to become non-achievers to LDL-C target. It is also important to identify underlying socioeconomic and lifestyle-related factors in order to begin appropriate interventions and management.

Our primary health care setting has a vast array of patients charactheristic with demographic differences, patients from the rural areas, semiurban area as well as urban area seeking treatment in the same facility. The information obtained from this study is useful for the health care providers to evaluate the achievement of cholesterol level and medication adherence in their own health care setting .

CHAPTER 2

LITERATURE REVIEW

2.1 LDL-C target in Dyslipidaemia and Type 2 Diabetes Mellitus

In Clinical Practice Guidelines on Management of Dyslipidaemia 2011, the optimal primary target of LDL-C value is dependent upon the patients assessment of global cardiovascular risk factors(13). NCEP-ATP III recognised three risk group categories and the LDL-C target is dependent upon to the risks that fall into(14). The three risk groups are low risk(≤1 risk factor), moderate risk(>2 risk factors) and high risk category (CHD and CHD risk equivalents), where in their LDL-C target are <4.1mmol/l, <3.4mmol/l and <2.6mmol/l. The target for patients with dyslipidaemia and Type 2 Diabetes Mellitus in accordance to NCEP-ATP III is <2.6mmol/l and this target is similar to the American Diabetes Association(ADA)(15).

Canadian Diabetes Association(CDA) stated in the 2008 practice guideline that the LDL-C target for Type 2 Diabetes Mellitus is ≤2.0mmol/l which is much lower than NCEP-ATP III(16). European Atherosclerotis Society/ European Society of Cardiology(EAS/ESC) recommended the primary LDL-C target for patients with very high risk and high risk as<1.8mmol/l and <2.5mmol/l(17). American College of Cardiology/ American Heart Association(ACC/AHA) published its latest guideline in 2013 for the treatment of blood cholesterol to reduce risk of Atherosclerotic Cardiovascular Disease(ASCVD) in adults;

raising many controversial issues(18). In the guideline, there is no target of LDL-C and patients will be treated according to the four statin benefit group. There will be three options of treatments for these group of patients which encompass high intensity statin, moderate intensity statin and low intensity statin. Patients with comorbid Dyslipidaemia and Type 2 Diabetes Mellitus will be classified under the group that needs be treated with high intensity statin(atovastatin 40mg to 80mg or Rosuvastatin 20mg).

2.2 Statin therapy in dyslipidaemia

Statins are the most effective drug class and is the treatment of choice in reducing Low Density Lipoprotein Cholesterol and they also have an additional effect of antiatherosclerothic propeties(13, 14, 17). It inhibits 3-Hydroxy-3methyl glutaryl coenzyme A Reductase (HMGCoA Reductase) in the liver and limits the rate of hepatic cholesterol synthesis. It is used as the first line agents in Familial Hypercholesterolemia, primary prevention of cardiovascular disease, secondary prevention of cardiovascular disease and coronory heart disease equivalents(13, 19, 20). A natural compound with inhibitory effect towards HMG-CoA Reductase was discovered in 1970s by Japanese microbiologist, Akira Endo in a fermentation broth of Penicillium citrinum during a search for antimicrobial agents(21). Lovastatin was the first statin to be developed and later followed by simvastatin in 1988, pravastatin in 1991, fluvastatin in 1994, atorvastatin in 1997 and resuvastatin in 2003. The mean reduction of LDL-C level with the maximal recommended dose of different statin ranges from 35% to 55%(14).

Many landmark clinical trials have shown the benefits of statins for primary and secondary prevention(22-26). These benefits were evident in patients with coronary heart disease and high or normal blood cholesterol concentrations, as well as in asymptomatic patients at increased risk of coronary heart disease. The instances of studies conducted encompassed Scandinavian Simvastatin Survival Study(4S) , Long-term Intervention with Pravastatin in Ischemic Disease(LIPID), Cholesterol And Recurrent Events trial(CARE), West of Scotland Coronary Prevention Study(WOSCOPS) and Air Force/Texas coronary atherosclerosis Prevention Study (AFCAPS/TexCAPS).

In 4S study, 4444 patients with angina pectoris or previous myocardial infarction and serum cholesterol 5.5-8.0 mmol/L on a lipid-lowering diet were randomised to double-blind treatment with simvastatin or placebo(23). This study showed that long-term treatment with simvastatin is safe and improves survival in CHD patients. Sacks *et al* studied the effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels demonstrated that the benefit of cholesterol-lowering therapy extends to the majority of patients with coronary heart disease who have average cholesterol levels(19). AFCAPS/TexCAPS study was conducted in year 1998 in a healthy individual with average serum cholesterol level treated with Lovastatin 20-40mg ON(22). The reduction of LDL-C by 25% was noted and the incidence of first acute major coronory events in men and women had significantly reduce (183 vs 116 first event;Relative Risk[RR],0.6;95% Confidence Interval[CI]0.5-0.79;P<0.01)(22).

2.2 LDL-C Achievement and its associated factors

Many studies had been investigating into the LDL-C achievement in patients with cardiovascular risk factors or patients with cardiovascular disease(27-29). Despite the effectiveness of lipid lowering agents with specific preference for statin, the results of attainment of LDL-C by patients varied in each study. A multinational study examined patients with different risk categories found that a good percentage of patients attained their LDL-C which in overall was 73%(30). The researchers also found that most of the achievers of LDL-C goal attaintment(74%) belong to the low risk category. The predictors to the success rate were lipid lowering therapy, lower risk group, geographic region, male gender, older age, race, absence of dietary counselling, diabetes and hypertension(30).

An almost identical study was done by Al-Khateeb *et al* which looked into the attaintment of LDL-C among patients with dyslipidaemia in Malaysia(28). They also discovered that low risk group had achieved their cholesterol target better than the high risk group and lower baseline LDL-C value was also inversely related to therapeutic goal attainment(28). The results from the National Cholesterol Education Programme Evaluation Project Utilizing Novel E Technology II (NEPTUNE II) showed evidence of ethnic differences in achievement of cholesterol treatment goals(31). NEPTUNE II was conducted among a group of patients treated with statin therapy which were recorded in the patients personal medical database. In the study, they concluded that the low achievers in LDL-C goal attainment among Africans American was due to less aggressive management in this ethnic group and suboptimal compliance. The other predictors of the treatment success found in this study were gender, obesity, level of triglycerides, diabetes, high efficacy statin therapy used and compliance to diet therapy.

The undertreatment of LDL-C was investigated in a study done by Pearson *et al*. They looked into the awareness among the physicians of the NCEP guidelines and how well these guideline were being implemented in their clinical practice(32). It was also called the Lipid Treatment Assessment Project(L-TAP) with the main objective of looking for utilization of lipid lowering therapy in the primary care practitioners(32). The LDL-C achievement in patients with coronory heart disease were very low(18%) and researcher found that the physicians tended not to titrate the dose of statin or use combination therapy. This was an old study done in 1997 in the era in which potent statin such as atorvastatin was still unavailable.

An interventional study by Afonso *et al* evaluated the effectiveness of patient education programme and provider awareness and the impact toward improvement in LDL-C attainment(33). The study discovered that only 35.5% of patients achieved their LDL-C target at baseline which later increased to 59.8% after the intervention programme and 97.3% of the achievers were patients with higher level of adherence to medication. The intervention was a single 15 minutes session individual education by a trained research assistant. The information provided were cholesterol content in food, a low cholesterol diet, the importance of medication adherence and risk associated with hyperlipidaemia. The subjects were patients with higher risk for cardiovascular event such as CHD, DM, multiple risk factors that confer a 10-year risk for coronory artery disease more than 20% or other clinical forms of atherosclerotic disease(33). The LDL-C target achievers were those in older age group and who consumed a greater number of medications compared to the nonachievers. Patients' education is very important as it can improve their knowledge, awareness about diseases and built up self empowerment.

2.3 Medication adherence

Compliance, adherence and persistance are the terms that always been used in the literature to describe the behaviour of medication consumption(34). Currrently, the term adherence has become a preferred term because it describe the agreement of medication taking behaviour between patient and physician(35). It is well known that adherence plays an important role in management of disease to make the treatment productive and yields satisfactory outcome in the end. Many studies had demonstrated that the causes of the nonadherence can be due to cost of the drug, side effect of the drug, scepticism towards the effectiveness of the drug, improved conditions as well as consumption of too many prescription(36-39).

Nonadherence to medications is common for patients with chronic illnesses such as cardiovascular disease, diabetes, hypertension and dyslipidaemia. According to the World Health Organisation, nonadherence with long term medication for conditions such as hypertension, dyslipidaemia and diabetes is a common problem that leads to compromised health benefits and serious economic consequences in term of wasted time, money and uncured disease(40). One review article found the nonadherence toward medication was 41% overall, 36% for antihypertensives, 42% for antidiabetics and 49% for lipid lowering agents(38). Natarajan *et al* conducted a patient self report survey at primary care clinic to measure patients adherence to statin therapy using a 4 item Morisky Scale. The rate of nonadherence to statin therapy showed a lower rate of nonadherence which was 37%(41).

Another study by Birmingham *et al* at different primary care setting found approximately about 51% patients were not adhered to statin therapy and one quater of it described as intentional which meant it arises from patients' decisions based on their health experiences and beliefs(42).

2.3.1 Measurement of medication adherence

World Health Organization 2003 described adherence as a multidimensional phenomenon which is determined by five set of factors including socioeconomic factor, health care system, condition related, therapy related, and patient related(40). Adherence can be assessed through several different ways. Adherence to medication can be assessed either through direct methods or indirect method. The examples of direct method are direct observed therapy, measurement of the level of medicine or metabolite in the blood and measurement of the biological marker in the blood. The examples of indirect methods are patient's questionnaire / patient's self report, rate of prescription refills, pill counts, assessment of the patient's clinical response, electronic medication monitors, measurement of physiologic markers and patients' diaries(43). Systematic review of an article by Vermiere *et al* found that direct method is the most accurate method to assess adherence(43).

Measurement level of medicine and markers in blood are the most accurate method but it is invasive, unacceptable and costly. Direct Observe Therapy is also an accurate method but it is not practical to be applied to all kind of disease as it involved more human resources and need patients' commitment. Indirect method is more frequently used worldwide especially in medical research. Interview and all self reported methods are vulnarable to overestimates of

compliance and underestimate of noncompliance(43). Questionnaires and diaries were found to be moderate to highly concordance to with most of other measure of medication adherence(44). However, interview based self reporting less likely to be concordance with nonself report medication adherence(44).

The most commonly used in the study are rate of prescription refills (propotion of days covered (PDC)/ Medication Possesion Rate(MPR) and 4 or 8 item Morisky Medication Adherence Scale (MMAS)(35). Prescription refill dates such as Medication Possession Ratio(MPR) or Medication Refill Adherence(MRA) depends on the completeness of the pharmacy database and counting tablet given to patients often overestimates compliance(43). Electronic devices or Medication Event Monitoring System(MEMS) also provide more accurate method for adherence measurement. This system enables both frequency and times of opening the medication bootle to be measured(43). MEMS led to discovery of 'drug holidays' or 'white coat adherence' where the patient's adherence pattern correlate with the time to meet physicians. Medication Compliance Questionnaire(MCQ) is a newly developed and validated tool to be used in assessing adhenrence to medication and was found useful to be used in patients with chronic illnesses(45). Despites of presence of various method in measurement medication adherence, there is still no definite gold standard method(35). However, indirect method was preferable as it more convenient and easy to be adminstered.

2.3.2 Predictors to poor adherence to medication

Many studies have looked into factors that influenced poor adherence towards medications. Few major predictors that have been described by various studies include side effects of medication, presence of cognitive impairment, treatment of asymptomatic disease, missed appointments, complexity of treatment and poor provider-patients relationship(35). Richard *et al* studied the adherence pattern among patients with co-morbid hypertension and dyslipidaemia. The major predictors for adherence noted in this study were patients who were initiated with both antihypertensive and antilipid therapy, patients with previous coronory artery disease or congestive cardiac failure and also patients who took less medication(46).

Study by Stilley *et al* looked into the relationship between psychological and cognitive function with adherence to cholesterol lowering therapy and found that estimated IQ were the strongest predictors of medication adherence(47) . Mood and personality did not not illustrate any significant relationship with medication adherence. Likewise, demographic characteristics such as income and education level in that study were indicated as not significantly related to medication adherence.

However, Natarajan *et al* described the younger patients between 40 to 54 years old tend to adhere less to statin therapy compared to patients of 65 years old and above(41). The study also discovered that the patient's belief and perceptions towards medications gave an impact towards the effect of the medication; if the patients believed by taking statins lower their risk of getting heart attacks or strokes, they will adhere better to statin therapy.

2.4 LDL achievement and adherence

National Cholesterol Education Programme(NCEP) has established LDL-C as the primary target of therapeutic intervention and the target level of LDL-C will be based on individual cardiovascular risk. In patients with Type 2 Diabetes Mellitus, the recent NCEP Adult Treatment Panel III guidelines stated that the target level is less than 2.6mmol/l.

Afonso *et al* studied the achievement of LDL cholesterol level in high risk patients. The study evaluated the effectiveness of combined intervention targeting the patients and the providers(33). The interventions include educating patients regarding their cholesterol level, risk factors and medication adherence. It is demonstrated that these combined interventions were successful in improving adherence to medication and at the same time improved the LDL-C goal attaintment. Eventhough many studies looking into medication adherence, the relationship between medication adherence and achievement of LDL-C target is still underexamine.

CHAPTER 3

OBJECTIVES

3.1 General Objectives

To determine the proportion of patient achieving target of low density lipoprotein cholesterol, the associated factors to nonachievement of LDL-C target and adherence to statin therapy among patients with Type 2 Diabetes Mellitus.

3.2 Specific objectives

1.   To determine the proportion of low density lipoprotein cholesterol target level achievers and nonachievers among patients with Type 2 Diabetes Mellitus.

2.   To determine the percentage of patients' adherence to statin therapy among patients with Type 2 Diabetes Mellitus.

3.   To determine the associated factors to nonachievement of LDL-C target among patients with Type 2 Diabetes Mellitus.

3.3   **RESEARCH HYPOTHESIS**

Sociodemographic and clinical factors including nonadherence to statin therapy are associated with the nonachievement of LDL-C target.

3.4 **Operational definition**

1. Low density lipoprotein cholesterol(LDL-C) achievement is based on the National Cholesterol Education Programme −Adult Treatment Panel III. This study only measured the general LDL-C target for patients with Type 2 Diabetes Mellitus in accordance to the guideline which is less than 2.6mmol/l. The achievers for LDL-C target are grouped as below:

(i) LDL-C target achievers = diabetic patients who attained LDL-C level < 2.6mmol/l

(ii)LDL-C target nonachievers = diabetic patients who attained LDL-C level ≥2.6mmol/l

2. A patient is considered to adhering to medication if he/she scored a total percentage of

$\geq 75\%$ in Medication Compliance Questionnaire. We devided the category of adherence in our study as below:

i-   Fully adhered: patients who attained 100% score in MCQ

ii-   Adhered: patients who attained ≥75% score in MCQ

iii-   Nonadhered: patients who attained <75% score in MCQ

CHAPTER 4

METHODOLOGY

4.1 Study design

This is a cross sectional study.

4.2 Study area

This study was conducted in Klinik Rawatan Keluarga(KRK), Hospital Universiti Sains Malaysia(HUSM) which is situated in Kubang Kerian, Kelantan. HUSM also a centre for referral for whole state of Kelantan. Klinik Rawatan Keluarga is an outpatient clinic and is run by 50 staffs including the Family Medicine Lecturers, the Family Medicine Specialist in training, medical officers and nurses. Daily attendance in KRK ranges from 200 to 300 patients. KRK is an integrated clinic and Diabetes Mellitus is one of the major chronic illness who visit KRK.

4.3 Population and sample

4.3.1 Reference population

Reference population was the patients with Type 2 Diabetes Mellitus in Kelantan.

4.3.2 Source population

Source population was the patients with Type 2 Diabetes Mellitus attending Klinik Rawatan Keluarga in Hospital Universiti Sains Malaysia.

4.3.3 Study population

Patients with Type 2 Diabetes Mellitus who attended Klinik Rawatan Keluarga in Hospital Universiti Sains Malaysia from January 2013 to May 2013 and fulfilled the inclusion and exclusion criteria.

4.3.4 Inclusion criteria

1. Age 18 years old and above.

2. Patient diagnosed with Type 2 Diabetes Mellitus.

3. Patient diagnosed with Dyslipidaemia.

4. Duration of undergoing statin therapy were more than 6 months.

4.3.5 Exclusion Criteria

1. Patient with psychiatric illness or mental retardation.

2. Unable to read or write.

3. Triglycerides > 4.3mmol/l

4.3.6 Sampling method

Systematic random sampling in the ratio 1:2 based on patient attendance list for blood taking in KRK.

4.3.7 Sample size calculation

Sample size was calculated for all the objectives. However, the one that yield the biggest number was taken as the sample size. The probability of non-respond, drop out or missing data was 30%.

Objective 1: To determine the proportion of low density lipoprotein cholesterol target level achievers and nonachievers among patients with Type 2 Diabetes Mellitus.

Calculation of sample size using **formula single proportion**.

$n = (z / \Delta)^2 \, p \, (1 - p)$

n = minimum required sample size

z = value of standard normal distribution = 1.96

Δ = absolute precision = 0.07

p = anticipated proportion of LDL-C achievers (48)

p = 0.44

   n= 193

   n + 30% drop off = 251

The minimum sample size calculation is 193 and after considering 30% non respondent, the sample size is 251.

Objective 2: To determine the patients' adherence toward statin therapy among patients with Type 2 Diabetes Mellitus.

Calculation of sample using **formula single proportion.**

$n = (z / \Delta)^2 \, p \, (1 - p)$

n = minimum required sample size

z = value of standard normal distribution = 1.96

Δ = absolute precision = 0.07

p = anticipated proportion of adherence to statin (41)

p = 0.37

n=180

n+30% drop off =234

The minimum sample size calculation is 180 and after considering 30% of the non respondent, the sample size is 234.

Objective 3: To determine the associated factors to nonachievement of LDL-C target among patients with Type 2 Diabetes Mellitus.

Categorical variables

The sample size calculation was done using Power and Sample Size Calculation software. The calculation of sample size was as follows:

α   Level of significant = 0.05

Power   0.8

Po   0.47(Proportion of LDL achievers among male patients)(42)

P_1 0.67 (expected proportion of LDL nonachievers among male patients)

m = 1

The sample size shown by the PS Software= 95, Therefore the final number of sample requirred is 95(1+1) =190. After considering the non-respond rate of 30%, the number of patients needed in this study was 247.

<u>Numerical variables</u>

The calculation of the sample size was as follows:

α   = 0.05

Power   =0.8

σ   = 9.2(standard deviation of mean age in LDL-C nonachievers)(42)

δ   = 5(expected detectable difference mean age of LDL-C achievers and LDL-C

nonachievers)

m   1

Sample size by shown by PS Software= 54, Therefore the final number of sample requirred is 54(1+1) =108. After considering the non-respond rate of 30%, the number of patients needed in this study was 140.

Table 4.1 Sample size culculation for categorical variables

Variables	P_0	P_1	Minimum sample size(n)	n+30%
Gender(42)	0.47	0.67	190	247
Adherence group(42)	0.59	0.39	194	252

Table 4.2 Sample size culculation for numerical variables

Variables	σ	δ	Minimum sample size(n)	n+30%
Age	9.2	5	108	140
BMI	3.6	2	104	135
SBP	19.6	10	122	158
DBP	12	8	190	247

The biggest sample size belongs to **objective 3** which was **252**. In this study, the sample size of **252** was used.

4.4 Research tools

The research tools consisted of:

1) Case report Form. This section was filled up by interviewer.

    a. Socio demographic data consists of information regarding age; sex; race; marital status; smoking status; occupation; income and education level.

    b. Clinical data information including medications (number of medications and type of statin), investigations result (lipid profile and HbA1c) and examinations (weight, height and blood pressure).

2) Self administered questionnaires. This section was filled up by study subjects.

    a. Patient's treatment data which includes information about the duration anticholesterol medication consumption, knowledge and side effects of anticholesterol medication consumed.

    b. Medication adherence questionnaire: Medication Compliance Questionnaire(MCQ) was used in this study. It was developed by Hassan et al in 2006 to assess adherence towards antihypertensive medication(45). It is comprised of a set of 10 questions which consists of 2 domains: a drug taking behaviour domain comprising 7 items and a drug stopping behaviour domain comprising 3 items . The internal consistency realibilies (cronbach alpha) were 0.67 and 0.84 and test-retest single measure intraclass correlation coefficient were 0.78 and 0.83. The scores are calculated using the Likert scale ranging from 1 to 5 with 1 indicating 'never' and 5 indicating 'very frequent'. All negatively worded scores were reversed and all scores were converted to 0 to 100 score. Patient with good compliance or adherence with a score of $\geq 75\%$ correspond with ' frequently' and 'very frequently' for all item in the questionnaire.