COMBINATION THERAPY FOR OPTIMUM GLYCAEMIC CONTROL : A RANDOMIZED OPEN LABEL TRIAL COMPARING ROSIGLITAZONE WITH COMBINATION SULPHONYLUREAS AND METFORMIN TABLETS IN TYPE 2 DIABETES MELLITUS

by

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LIST OF ABBREVIATIONS

BMI	:	body mass index
DCCT	:	Diabetes Control and Complication Trial
DECODE	:	Diabetes Epidemiology : Collaboration Analysis of Diagnostic Criteria in Europe
FBS	:	Fasting blood sugar
HbA1c	:	haemoglobin A1c
HDL	:	High density lipoprotein
IGT	:	Impaired glucose tolerance
LDL	:	Low density lipoprotein
NGT	:	Normal glucose tolerance
SU	:	Sulphonylureas
TC	:	Total cholesterol
TG	:	Triglycerides
TZD	:	Thiazolidinediones
T2DM	:	Type 2 diabetes mellitus

UKPDS	:	United Kingdom Prospective Diabetes Study
WHO	:	World Health Organization
OR	:	Odd ratio
RM	:	Ringgit Malaysia

ABSTRAK

TERAPI KOMBINASI UNTUK KAWALAN GLUKOSA YANG OPTIMA : KAJIAN RAWAK SECARA TERBUKA MEMBANDINGKAN ROSIGLITAZONE DENGAN KOMBINASI SULPHONYLUREAS DAN METFORMIN DI DALAM PESAKIT DIABETES

Latar belakang

Seperti yang telah diketahui, untuk mencapai tahap glukosa yang di ingini dalam perawatan diabetes adalah bukan perkara mudah. Kombinasi beberapa ubat adalah di perlukan pada kebanyakan pesakit. Kombinasi ubat yang sering digunakan melibatkan perembes insulin dan ubat yang mengurangkan rintangan insulin. Penggunaan dua jenis ubat yang mengurangkan rintangan insulin tetapi dengan mekanisma kerja yang berbeza mungkin boleh memberikan kawalan glukosa yang lebih optima. Dengan menambahkan thiazolidindion mungkin membolehkan pencapaian tahap glukosa yang lebih baik kepada pesakit yang gagal mencapai tahap glukosa yang optima dengan kombinasi metformin dan sulphonilureas. Data mengenai efikasi, keselamatan serta keberkesanan kos di dalam penambahan agen ke tiga kepada pesakit yang gagal mencapai tahap glukosa yang maksima masih kurang.

Objektif

Objektif kajian ini adalah untuk menentukan efikasi, keselamatan dan keberkesanan kos dalam penambahan rosiglitazon kepada pesakit diabetes yang tidak mencapai tahap glukosa yang optima dengan maksima dos sulphonilureas dan metformin.

Kaedah kajian

Ini adalah kajian rawak secara terbuka. Pesakit yang gagal mencapai kawalan glukosa optima dengan kombinasi metformin dan sulfonilureas serta menolak rawatan insulin dibahagikan secara rawak kepada kumpulan rawatan dan kumpulan kawalan. Kumpulan rawatan menerima tambahan rosiglitazone 4 mg sekali sehari untuk jangkamasa 6 bulan manakala kumpulan kawalan mengekalkan metformin dan sulphonylureas dengan dos maksima. Profil paras HbA1c, paras glukosa berpuasa, profil kolesterol (TC, LDL dan HDL) diambil pada hari permulaan dan pada 6 bulan selepas randomisasi.

Keputusan

Sejumlah 75 pesakit diabetes terlibat di dalam kajian ini. Di dapati penurunan paras HbA1c (9.61 ± 1.37 % kepada 8.20 ± 1.87 % ; $p < 0.001$) dan paras glukosa berpuasa (9.6 ± 3.69 mmol/l kepada 7.93 ± 3.46mmol/L ; $p= 0.002$) di dalam kumpulan rawatan selepas 6 bulan adalah signifikan. Di dalam kumpulan kawalan, di dapati penambahan paras HbA1c adalah signifikan (9.75 ± 1.33 % kepada 10.06 ± 1.77 % ; $p = 0.023$) tetapi tiada perubahan signifikan di dalam paras glukosa berpuasa (10.81 ± 3.38 mmol/L kepada 10.48 ± 3.29 mmol/L ; $p = 0.95$) selepas tempoh 6 bulan. Tahap

penurunan HbA1c dan tahap glukosa berpuasa adalah lebih ketara dan signifikan di dalam kumpulan rawatan berbanding kumpulan kawalan , masing – masing - 1.37 % vs + 1.70 % dan - 0.24 mmol/L vs + 0.41 mmol/L. Dua puluh lapan peratus pesakit (28 %, p< 0.001) (11/ 40) di dalam kumpulan rawatan mencapai HbA1c < 7 % dan tiada pesakit di dalam kumpulan kawalan. Untuk tahap glukosa, 51 % (p < 0. 001) (19/ 37) pesakit di dalam kumpulan rawatan mencapai tahap glukosa < 7 mmol/L berbanding kumpulan kawalan, hanya 12 % (3/ 25) pesakit mencapai tahap glukosa < 7 mmol/L selepas tempoh 6 bulan. Tiada perbezaan yang signifikan di dalam profil kolesterol pada ke dua – dua kumpulan dalam tempoh 6 bulan.

Untuk setiap pertambahan tahap HbA1c > 1 %, di dapati 13.3 kali peluang untuk mencapai tahap HbA1c yang lebih baik (OR 13.3, adjusted 17). Nisbah keberkesanan kos di antara ke dua- dua kumpulan adalah tidak signifikan (z = -0.79, p = 0.43).

Kesimpulan

Penambahan rosiglitazon membaiki tahap glukosa, bila dibandingkan dengan pesakit di dalam kumpulan kawalan, membolehkan lebih pesakit mencapai HbA1c < 7 % dengan penurunan HbA1c yang lebih signifikan. Penambahan rosiglitazon kepada pesakit yang telah pun mendapat metformin dan sulphonilureas maksima dos adalah berefikasi tetapi tidak ada keberkesanan kos.

ABSTRACT

COMBINATION THERAPY FOR OPTIMUM GLYCAEMIC CONTROL: A RANDOMIZED OPEN LABEL TRIAL COMPARING ROSIGLITAZONE WITH COMBINATION SULPHONYLUREAS AND METFORMIN TABLETS IN TYPE 2 DIABETES MELLITUS

Background

As it is often difficult to achieve and maintain glycaemic goals, multiple drug therapy is eventually required in most patients. Combination therapy, involving an insulin secretagogue and an insulin sensitizer, can address the metabolic effect of this disease. The use of two sensitizers with different but complementary mechanisms of action may provide additional glucose control. The addition of thiazolidinedione may improve glycaemic control in patients who failed to achieve glycaemic control with a combination of sulphonylureas and metformin. There is scarce data on efficacy, safety and cost effectiveness of adding third agent to patients who failed to achieve glycaemic control on maximum combination therapy.

Objectives

To determine the efficacy, safety and cost effectiveness of adding Rosiglitazone to patients with type 2 diabetes mellitus on maximum dose of sulphonylureas and metformin who had not achieved glycaemic control

Research design and methodology

This was a randomized, open label study. The subjects with T2DM who refused insulin therapy were randomized into treatment group and control group. The treatment group received adding a dose of rosiglitazone 4 mg once daily for 6 months while the control group was maintained on maximum dose of metformin and sulphonylureas. HbA1c, FBS, Total Cholesterol, LDL and HDL were taken at baseline and at 6 month.

Results

A total of 75 diabetic patients were included in this study. There was significant reduction in HbA1c (9.61 ± 1.37 % to 8.20 ± 1.87 % ; $p < 0.001$) and FBS (9.6 ± 3.69 mmol/L to 7.93 ± 3.46mmol /L ; $p = 0.002$) in treatment group after 6 months of therapy. However, in control group, there was a significant increased in HbA1c (9.75 ± 1.33 % to 10.06 ± 1.77 % ; $p = 0.023$) but no significant change in FBS (10.81 ± 3.38mmol/L to 10.48 ± 3.29 mmol/L ; $p = 0.95$) at 6 months. There was greater reduction in HbA1c level and FBS in treatment group compared to control group - 1.37 % vs + 1.70 % and - 0.24 % vs + 0.41 % respectively. Twenty eight percent (28 % ; $p < 0.001$) (11 / 40) of patients of the treatment group achieved HbA1c < 7 % while no one in control group achieved this target. For FBS, 51 % ($p < 0.001$) (19 / 37) of patients in the treatment group achieved FBS < 7mmol/l compared with the control

group, only 12 % (3 / 25) of patients achieved FBS < 7 mmol/l at 6 months. There were no significant changes in lipid profiles at 6 months in both groups.

In addition, for every improvement of 1 % HbA1c, there was 13.3 times better chance in improvement of HbA1c (OR 13.3, adjusted 17). The cost effectiveness (CE) ratio between the treatment and the control group was not significant (z = - 0.79, p= 0.43)

Conclusion

The addition of rosiglitazone improves glycaemic control, when compared to patients in control group, allowing more patients to achieve HbA1c < 7 % with greater reduction of HbA1c. In addition, adding rosiglitazone to patients on maximum metformin and sulphonylureas were efficacious but not cost effective.

CHAPTER ONE

CHAPTER ONE

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by pancreatic beta cell dysfunction and insulin resistance in the liver, skeletal muscle cell and adipose tissue (DeFronzo, 1999). It is increasing in frequency such that it is now considered as a worldwide epidemic. Approximately 100 million people worldwide were reported to have the disease in 1994, and this figure is expected to more than double to 215 million by the year 2010 (Zimmet *et al,* 2001). The therapeutic goals are to return glycemic control to normal and prevent emergence of long-term complications.

1.1 Diagnosis

Diabetes mellitus is diagnosed on the basis of WHO recommendations from 1999, incorporating both fasting and 2-h after glucose load (75 g) criteria into a practicable diagnostic classification that should now be used (table 1.1). Conditions that predispose to overt diabetes, including impaired fasting glucose and impaired glucose tolerance are not merely of academic interest, since, unless treated, about 7% of people with these problems will progress to overt diabetes every year. (Tuomilehto *et al,* 2005) Furthermore, impaired glucose tolerance itself carries an increased risk of macrovascular disease (DECODE Study Group, 1999).

Table 1.1. Diagnostic criteria of diabetes mellitus and other categories of hyperglycaemia

	Glucose concentration in venous plasma (mmol/L)
Diabetes mellitus	Fasting ≥ 7.0 or 2 h post glucose load 11.1
Impaired glucose tolerance	Fasting(if measured)<7.0 and 2 h post glucose load ≥ 7.8 and < 11.1
Impaired fasting glucose	Fasting ≥ 6.1 and < 7.0 and 2 h post-glucose load (if measured) < 7.8

Glucose load = 75 g glucose orally

1.2 Pathophysiology of type 2 diabetes

To understand the cellular and molecular mechanisms responsible for T2DM it is necessary to conceptualize the framework within which glycaemia is controlled. Insulin is the key hormone for regulation of blood glucose and, generally, normoglycaemia is maintained by the balanced interplay between insulin action and insulin secretion. Importantly, the normal pancreatic beta cell can adapt to changes in insulin action i.e., a decrease in insulin action is accompanied by upregulation of insulin secretion (and vice versa). Figure1.2. illustrates the curvilinear relation between normal beta cell function and insulin sensitivity (Bergman , 1989). Deviation from this hyperbola, such as in the patients with impaired glucose tolerance and T2DM, occurs when beta cell function is

inadequately low for a specific degree of insulin sensitivity. Thus, beta cell dysfunction is a critical component in the pathogenesis of T2DM. This concept has been verified not only in cross-sectional studies but also longitudinally in Pima Indians progressing from normal to impaired glucose tolerance to T2DM (Weyer *et al*, 1999). However, not only deviation from but also progression along the hyperbola affects glycaemia. When insulin action decreases (as with increasing obesity) the system usually compensates by increasing beta cell function. However, at the same time, concentrations of blood glucose at fasting and 2 h after glucose load will increase mildly. (Stumvoll *et al,* 2003), This increase may be small, but over time becomes damaging because of glucose toxicity, and in itself a cause for beta cell dysfunction. Thus, even with (theoretically) unlimited beta cell reserve, insulin resistance paves the way for hyperglycaemia and T2DM.

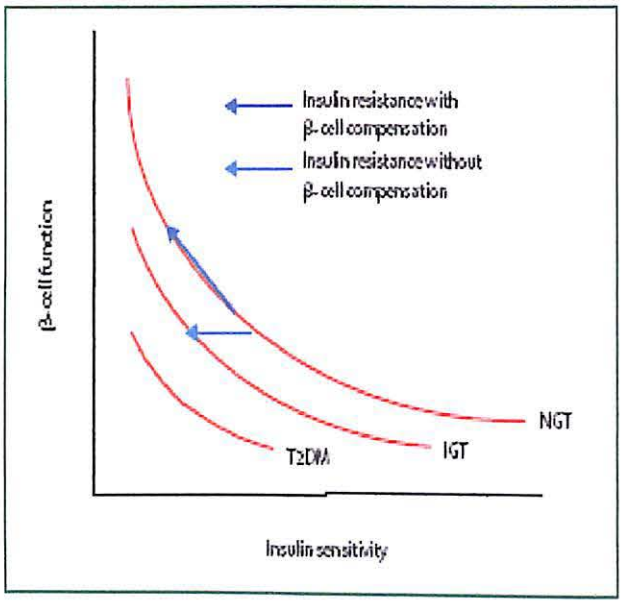

Figure 1.2. Hyperbolic relation between insulin sensitivity and beta cell function. In people with normal glucose tolerance (NGT) a quasi hyperbolic- relation exists between cell function and insulin sensitivity. With deviation from this hyperbola, deterioration of glucose tolerance (impaired glucose tolerance [IGT]) and T2DM occurs. Adapted from Stumvoll M, Barry JG, Timon W (2005)

1.2.1. Insulin resistance

Insulin resistance is said to be present when the biological effects of insulin are less than expected for both glucose disposal in skeletal muscle and suppression of endogenous glucose production primarily in the liver (Dinneen *et al,* 1992) In the fasting state, however, muscle accounts for only a small proportion of glucose disposal (less than 20%) whereas endogenous glucose production is responsible for all the glucose entering the plasma. Endogenous glucose production is accelerated in patients with type 2 diabetes or impaired fasting glucose. (Weyer et al, 1999: Meyer *et al,* 1998) Because this increase occurs in the presence of hyperinsulinaemia, at least in the early and

intermediate disease stages, hepatic insulin resistance is the driving force of hyperglycaemia of T2DM

1.2.2. Potential causes of beta cell dysfunction in Type 2 diabetes.

1) Reversible metabolic abnormalities

a) Glucotoxicity

Glucose toxicity is a concept that associates beta cell desensitization to glucose with increase blood glucose concentration (Robertson *et al,* 1994; Yki-Jarvinen, 1992). This has been demonstrated with in vitro and in vivo animal research (Weir *et al,* 1983; Trend *et al,* 1992) Lowering serum glucose levels in T2DM or impaired glucose tolerance can increase their acute response to glucose (. Mott *et al,*1993). Chronic hyperglycaemia may deplete insulin secretory granules from beta cells, leaving less insulin ready for release in response to new glucose stimulus. Lowering glucose levels allow regranulation of beta cells, and thus, better insulin response.

b) Lipotoxicity

Lipotoxicity has deleterious effects on beta cells of accumulated fatty acids and their metabolic products that are observed among individuals with insulin resistance , glucose intolerance and T2DM. Evidence leading to this hypothesis includes data from in vitro and in vivo animal studies (Zhou *et al,* 1998; Unger *et al,* 1995, 2001). Fluctuations of free fatty acid levels are necessary for normal beta cell function but prolonged increase in their levels have a negative impact on the conversion of proinsulin to insulin and thus on insulin secretion (Zhou *et al,* 1995 ; Grill *et al,* 1994, Sako *et al,* 1990) . The

extent to which lipotoxicity contributes to progressive beta cell failure that leads to diabetes is still unknown.

2) Reduction of beta cell mass

A reduction in beta cell mass has been observed in people with T2DM (Kloppel *et al,* 1985 ; Janssen *et al* , 2003) and impaired glucose tolerance compared with people who are equally obese but have normal glucose levels. The exact cause is unknown and probably complex. It may relate to glucose or lipid toxicity whereby programme cell death (apoptosis) occurs in hostile metabolic and biochemical environment (Efanova *et al,* 1998) . In vitro and vivo animal studies have highlighted possible causes of reduced beta cell mass : impaired beta cell function, glucose intolerance and rising hyperglycaemia in conjunction with amyloid deposits and toxic amyloid fibrils (Jansson *et al,* 1999 ; Lorenzo *et al,* 1994). Interestingly, predisposing characteristic found in patients with T2DM are also observed in animal models for amyloid disposition, namely high fat diet and oestrogen depletion (Kahn *et al,* 2000; Manson *et al,* 1992; Marshall *et al,* 1992) .

Other potential causes are hormonal changes which includes inadequate incretin action and increased glucagons secretion and genetic abnormalities of beta cell proteins (glukokinase, insulin receptor, IRS – 1, HNF – 4 α).

2.0 The importance of Glycemic Control

It has never been clearer that hyperglycemia, as assessed by the hemoglobin A1c (HbA1c) measurement, is the prime cause of diabetic microvascular complications (retinopathy, nephropathy, and neuropathy) and plays a role in the premature and accelerated development of diabetic macrovascular complications (coronary artery disease, cerebrovascular disease, and peripheral vascular disease). The Diabetes Control and Complications Trial (DCCT) showed that with a 2% difference (9% vs. 7%) in the HbA1c level there was a 63% decrease in development of retinopathy, a 54% decrease in the development of nephropathy, a 60% decrease in the development of neuropathy, and a 41% decrease in the development of macrovascular disease in type 1 diabetic patients; furthermore, the incidence of these complications was low if the HbA1c level was maintained at 7%. In addition, the DCCT showed that if the HbA1c level was above 8%, the rate of development of microvascular complications accelerated dramatically; as a result, the ADA recommended that intensification of therapy was required if the HbA1c level was above 8% (DCCT, 1993).

The Kumamoto study demonstrated an association between glycemic control and chronic diabetic complications in T2DM. They used thin, insulin-requiring, Japanese type 2 patients and used a protocol similar to that used by the DCCT (Ohkubo *et al*, 1995). As expected, the outcomes were similar, with a 2.0% difference in HbA1c level being associated with a 69% decrease in retinopathy and a 70% decrease in nephropathy

The increasing use of HbA1c to monitor long-term glycemic control in diabetic patients is largely the result of data from the DCCT and the U.K. Prospective Diabetes Study

showing that HbA1c is strongly correlated with adverse outcome risks (UKPDS 33, 1998) .

3.0 Management of hyperglycaemia

In making therapeutic choices (Figure 1.3) in the management of T2DM, the major goal of protecting patients from the long-term complications of the disease must be considered. Because insulin resistance plays a fundamental role in the pathogenesis of type 2 diabetes and especially its adverse cardiovascular outcomes, interventions should initially be aimed towards improvement in tissue insulin sensitivity. This often involves lifestyle intervention, with modest exercise and weight loss, which clearly reduces the risk of progression of impaired glucose tolerance to overt diabetes (Diabetes Prevention Program Research Group , 2002: Tuomilehto *et al,* 2001) and can improve many of the cardiovascular risk parameters of the metabolic syndrome.

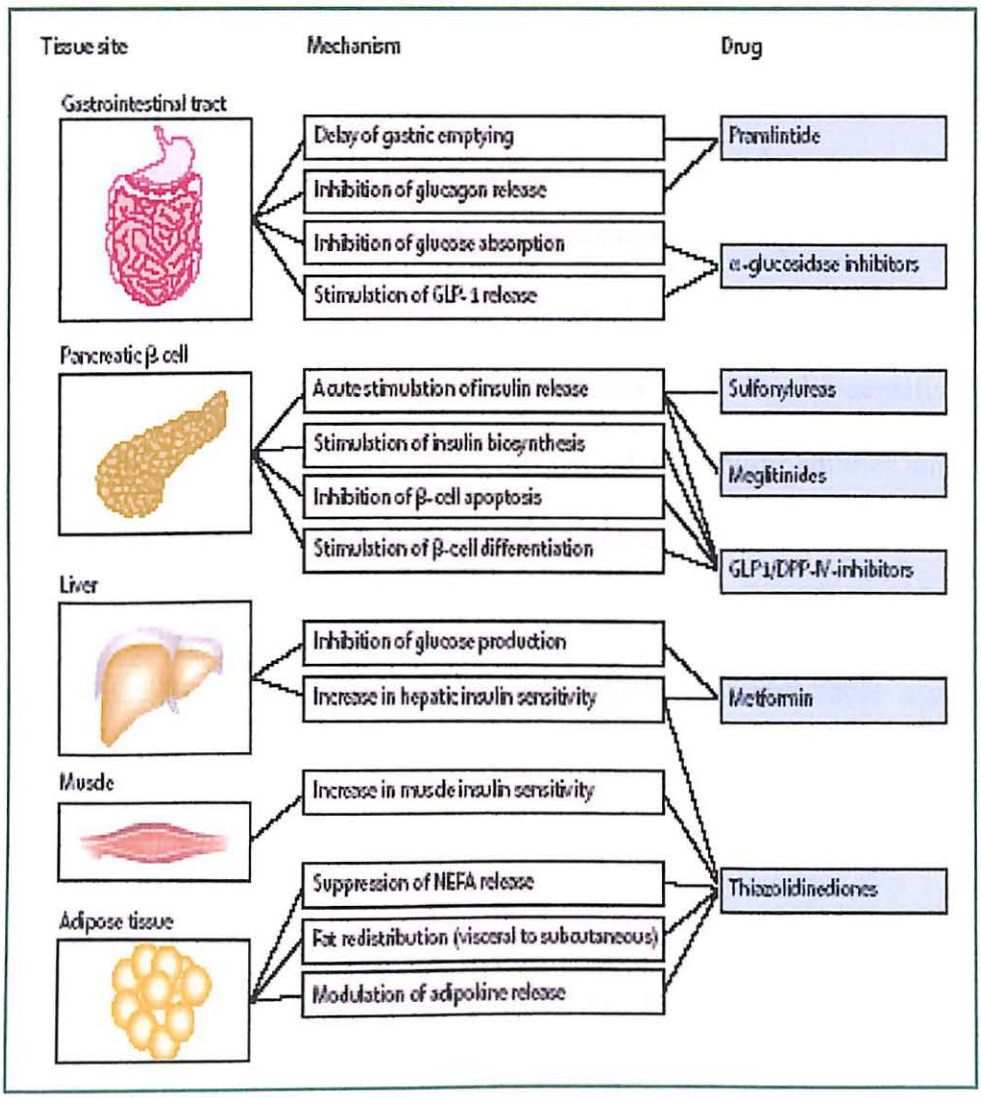

Figure 1.3. Pharmacological treatment of hyperglycaemia according to site of action.

Adapted from Stumvoll M, Barry JG, Timon W (2005)

1.4.1 Thiazolidinediones

Drugs that enhance insulin sensitivity are primarily those of the thiazolidinedione class, which not only reduce glycaemia, but also enhance vascular function and ameliorate the dyslipidaemia and inflammatory milieu of T2DM (Yki-Jarvinen *et al* , 2004) Thiazolidinediones primarily activate PPAR γ receptors in adipose tissue and alter

adipose metabolism and distribution. The redistribution of tissue triglyceride from visceral stores reduces levels of circulating fatty acid apparently by sequestration in a less lipolytic subcutaneous compartment.(Yki- Jarvinen *et al,* 2004). Thiazolidinediones also reduce circulating concentrations of pro-inflammatory cytokines that promote insulin resistance (eg, TNF α and interleukin 6) and at the same time increase concentrations of adiponectin, which has insulin-sensitising and anti-inflammatory properties. The multiple effects of thiazolidinediones on adipose tissue metabolism and cross-talk of these signals with liver and skeletal muscle, as well as pancreatic beta cells and the vascular endothelium, might account for the enhancement of insulin action and improvement in insulin secretion with these agents, as well as several beneficial effects on vascular function (Meriden *et al,* 2004). The renal and vascular benefits of thiazolidinediones have been demonstrated in controlled studies, for example, showing significant improvement in albumin excretion above that observed with a similar degree of glycaemic lowering with sulfonylureas. (Einhorn *et al,* 2004) Unlike metformin, the thiazolidinediones can be used in patients with reduced renal function, and they are better tolerated without significant gastrointestinal side effects.

A major adverse effect associated with clinical use of the thiazolidinediones is weight gain, which seems to be coupled to the effects of the drugs on adipose cell differentiation and triglyceride storage. Fluid retention is also linked to the PPAR γ-agonist activity of the thiazolidinediones, leading to peripheral oedema and a mild haemodilution in some patients. Fortunately, congestive heart failure is quite rare with use of thiazolidinediones, but remains a serious concern that requires caution in selection of patients to receive these agents (Nesto *et al*, 2003).

In addition, there is also increased adiposity, although some studies suggest relative sparing of visceral fat. All thiazolidinediones cause a slight increase in low-density lipoprotein (LDL) levels and a substantial increase in high-density lipoprotein (HDL) levels. Thus, the LDL-to-HDL ratio actually decreases. There is also a slight lowering of blood pressure.

Unlike other antidiabetic agents, the thiazolidinediones have a very slow onset of action. Although effects begin within 2 weeks, the maximal benefit of treatment is not seen for about 3 months (Meriden *et al,* 2004) When combined with insulin or with sulfonylureas, the onset and peak effect occur more rapidly, perhaps within 4 weeks (Horton *et al,* 1998; Fonseca *et al*, 2000).

1.4.2 Metformin

Metformin is a highly effective antihyperglycaemic drug that works independently of the pancreas, sparing insulin. It decreases hepatic glucose output and has been shown to have a beneficial effect on cardiovascular outcomes .(Bailey *et al,* 1996 : Cusi *et al,* 1996, Mamputu *et al,* 2003). Metformin has less robust effects on insulin resistance, inflammatory markers, and vascular function compared with the thiazolidinediones, but its benefit in abrogating some of the weight gain commonly observed with insulin-sensitisers and insulin secretion enhancers adds important value to this drug.

1.4.3 Sulfonylurea derivatives

As inadequate beta cell insulin secretion is fundamental to the development of hyperglycaemia in diabetes, insulin secretion enhancers also play an important role in control of blood glucose. Sulfonylurea derivatives act by closing pancreatic cell potassium channels, which leads to enhanced insulin secretion. The results of the UK Prospective Diabetes Study showed a clear risk reduction for the occurrence of microvascular complications by the use of sulfonylurea derivatives, while the risk reduction of macrovascular disease was around 16% (UKPDS 33, 1998). The mode of action of sulfonylurea derivatives implies that they also act at low concentrations of plasma glucose, which explains the potential of (occasionally severe) hypoglycaemia.

1.4.4 Combination drug therapy

One of the major lessons of the UKPDS was to demonstrate that treatment of non-insulin-dependent diabetes with a single agent is not sufficient to attain the target goal of therapy. Although the level of attained benefit in the pharmacologically treated group as compared with the diet-treated group was 0.9%, there was still a deterioration over 10 years to 7.9%, with no advantage for any one pharmacologic group (Turner *et al,* 1999) Clearly, these levels are far from the target of normal HbA1c.

No one drug is capable of normalizing HbA1c in the vast majority of patients. This is particularly true in view of the progressive deterioration in control demonstrated in monotherapy in the UKPDS. However, each class of drugs shows additive benefits when added to other classes. The most common combination therapies are a SU plus

metformin (UKPDS 33, 1998), a SU plus TZD (for persons with insulin resistance) (Einhorn *et al*, 2004; Fonseca *et al,* 2000) and metformin plus TZD (Fonseca *et al,* 2000, Einhorn *et al,* 2004). Oral agents from different classes have an additive effect; each consecutive oral agent achieves an additional 1 – 2 % reduction in HbA1c level relative to monotherapy (Inzucchi *et al,* 2002).

For most patients with T2DM, the combination of a TZD and metformin will reduce hyperglycemia, hyperinsulinemia, and insulin resistance, preserve β cell function, and improve other components of the metabolic syndrome (e.g., dyslipidemia, hypertension, central obesity). These combination also has been shown to significantly reduce fasting plasma-glucose concentrations and HbA1c compared with metformin alone (Fonseca *et al*, 2000 ; Gomez Perez *et al*, 2002).This derives from actions of metformin on the liver, resulting in reduced hepatic glucose production, and those of the TZD on the adipocyes, resulting in increased peripheral glucose disposal and whole body insulin sensitivity. Furthermore, there is evidence that the combination of a TZD with metformin attenuates the weight gain associated with TZD monotherapy (Fonseca *et al*, 2000 ; Gomez Perez *et al*, 2002). By initiating combination therapy early in the course of the disease, it is hoped that many of the vascular complications associated with insulin resistance and T2DM can be delayed or avoided.

On the other hand, even the combination of oral agents may fail to sustain desirable glycemic control because of declining circulating insulin levels secondary to progressive beta cell dysfunction. Clinical studies also showed that diabetes treatment with insulin sensitizers does not fully correct insulin sensitivity nor restore adequate glucose

tolerance in all cases, implying genetic and / or environmental factors may also influence the individual response to these drugs. Masugi *Z* in their vitro studies suggested that genetic variants of the PPAR γ gene may influence the drug efficacy of TZD (Masugi *et al*, 1999). At this stage of the disease, initiation of insulin is required, either as monotherapy or as an adjunct to oral agents to attain and maintain glycemic control.

1.5 The role of insulin

The natural history of T2DM is characterized by progressive impairment of insulin secretion, paralleled by progressive deterioration of glycaemic control. Typically, the association of a sulphonylurea to a pre existing insulin sensitizer is intended to address such metabolic imbalance. Eventually, *'secondary failure'* occurs, and the patient is shifted to insulin therapy (Francesco *et al,* 2005). However, whether sulphonylureas may accelerate the loss of pancreatic secretory capacity, by causing beta cell apoptosis, has not been addressed in clinical studies. Early insulin administration in recently diagnosed diabetic patients has been proposed as an alternative approach that may provide some kind of *'beta cell rest'* and / or protection from apoptotic stimuli (Alvarrsson *et al,* 2003).

The most compelling argument for the early use of insulin is the lack of any alternative when glycaemic targets are no longer attained with oral antidiabetic agents. It must be noted that intensive therapy in the UKPDS was beneficial overall despite an increase in weight gain, and thus it is inappropriate in most cases to withhold insulin because of this anticipated side effects (UKPDS 33 , 1998). The benefits of an intensive strategy in

microvascular complications were demonstrated clearly in UKPDS, although the benefit of macrovascular complications failed to reach significance. Insulin therapy did, however, yield a large mortality benefit in the context of acute myocardial infarction in The Diabetes Mellitus Insulin- Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, which is, at the very least, strongly suggestive of a beneficial effect on cardiovascular status in the long term (Malmberg, DIGAMI, 1997)

1.5.1 Why insulin therapy delayed in persons with type 2 diabetes ?

Persons with T2DM may favor the postponement of insulin therapy, usually because of concerns about associated weight gain, insulin resistance and fear of injection. Most clinicians will have known patients with whom insulin therapy appeared to lead to massive weight gain without significant improvements in glycaemic control , and early conversion to insulin is not a panacea for the insulin resistant patient.

Survey from cross- national Diabetes Attitudes, Wishes and Needs (DAWN) study which identify correlates of attitudes toward insulin therapy among patients with T2DM and provider showed that their attitude differ significantly across countries, controlling for individuals characteristics. In this survey, patients rate the clinical efficacy of insulin as low and would blame themselves if they had to start insulin therapy. Self-blame is significantly lower among those who have better diet and exercise adherence and less diabetes-related distress. Patients who are not managing their diabetes well (poor perceived control, more complications, and diabetes-related distress) are significantly more likely to see insulin therapy as potentially beneficial. Most nurses and general practitioners (50-55%) delay insulin therapy until absolutely necessary, but specialists

and opinion leaders are less likely to do so. Delay of insulin therapy is significantly less likely when physicians and nurses see their patients as more adherent to medication or appointment regimens, view insulin as more efficacious, and when they are less likely to delay oral diabetes medications.

Health providers should be aware of the importance in early introduction to insulin therapy. They should educate and motivate their patients regarding the need to start insulin early. Survey from DAWN also noted that diabetes related worries were common among patients (41 %) and providers recognized these worries but lack of resources (skill, time, adequate referral centre). These poor psychological well-being affected diabetic self care. These issue need to be address to achieve optimum diabetic management.

Several studies have shown that improving glycaemic control with insulin therapy has an improving effect on underlying insulin resistance, contradicting concerns that greater hyperinsulinaemia would increase insulin resistance (Riddle, 2002 ; Garvey *et al*, 1985). Additionally, conversion to insulin is usually preceeded by a period of hyperglycaemia when body weight is lost as a consequence of glycosuria (Makkimatila *et al,* 1999). Although insulin reverses this process, it does not in itself cause significant weight gain (Larger *et al*, 2001). While this fact may be of little comfort to those patients who find themselves getting heavier, it does indicate the beneficial effect of early introduction of insulin in treating diabetes.

1.6 Cost effectiveness analysis (CEA)

Cost effective analysis is a method comparing the health outcomes (effectiveness) and the net costs from a program or an intervention against other alternatives with similar health outcomes (Cariere *et al*, 2001). It measures health outcomes in real terms, such as mortality, disability or quality of life. The net costs from a program or intervention are the costs for providing the program and for committing the resources for treatments after subtracting the non - health benefits from the program measured in monetary terms. Decision makers would choose a program that is most effective and least expensive. Carrie *et al* in their article summarized CEA in several steps.

The first step is to state the program or the intervention to be evaluated. Such detailed questions as what are the objectives; what experimental designs are being applied to the program should be answered in advanced. The perspective from which the analysis is being conducted is an important consideration. The costs savings or benefit may have different values from different perspectives, as accost from one perspective may be a benefit from another perspectives. In the second step, all resources of relevant costs and benefits have to be identified in real terms. The net benefits or benefit- to- cost ratios is calculated, based on which choice of the intervention with optimum value of net benefit or benefit to cost ratio is followed. Investigators would like to include all costs and benefits, direct cost and benefits, indirect costs and benefits and intangible benefits.

In the third step, benefits are identified and valued. The results from step 2 are adjusted by a discount rate because the monetary values at present depreciate over time. It also

adjusts for the health outcomes in some circumstances. The adjustment for health outcomes depends on what the health outcomes are and how the values for health outcomes change with time. The interpretation of the results from CEA will depend on incremental cost effectiveness ratio defined by the additional cost of an alternative relative to its additional effectiveness, or the original net costs and effectiveness.

1.6.1 The role and use of outcomes assessments

Outcomes research is the field of study describing the ultimate (final) health events that occur as a result of a condition or its treatment (Kozma *et al*, 1993). Stated differently, outcomes research is the process by which health care interventions are evaluated in order to measure the extent to which a goal of therapy can be reached. One classic list of outcome measures compromised the five Ds (Johnson *et al,* 1996) : death, disease, disability, discomfort and dissatisfaction. Several of these D s reflect a patient QoL (quality of life). Addition of the sixth D (dollars) produces a comprehensive list of measures to assess outcomes of medical interventions.

The type of outcomes can be grouped into three categories :

- Clinical based outcomes
- Patient based outcomes - Patient QoL is important criterion in determining the success of medical intervention.
- Cost based / economic outcomes- include items such as prescription medications, physician visits, laboratory tests , adverse events and treatment failures.

1.6.2 Applications for outcome research

Outcomes data are useful in evaluating the effectiveness of health care interventions. Adding patient – centered and economic outcome to the traditional clinical outcomes provides a comprehensive assessment of treatment and service(A Grizzle *et al,* 2001). Outcome data may also be used to support and understand research conclusions. Formulary committees are beginning to incorporate outcome measures (i.e. cost effectiveness and QoL) in their decision making process. With third party payers assuming more authority for drug purchasers , pharmaceutical companies now need to provide additional evidence of drug benefits, including cost effectiveness ratios and improvement in QoL compared with competitors. Outcome research, therefore, becomes an important aspect of new product development, as pharmaceutical companies need to demonstrate more than clinical benefits.

CHAPTER TWO

CHAPTER TWO

OBJECTIVES

2.1 General Objectives

2.1.1. To determine the efficacy, safety and cost effectiveness of adding Rosiglitazone to patients with type 2 diabetes mellitus on maximum dose of Glibenclamide / Gliclazide and Metformin who had not achieved glycaemic control

2.2 Specific Objectives

2.2.1. To assess the reduction of HbA1c and fasting plasma glucose in patient treated with Sulphonylureas and Metformin combined with Rosiglitazone after 6 months duration

2.2.2. To compare the reduction of HbA1c between the group patients treated with Sulphonylureas and Metformin combined with Rosiglitazone and Sulphonylureas plus Metformin alone.

2.2.3 To establish incidence of hypoglycaemia in the group patient treated with Sulphonylureas and Metformin combined with Rosiglitazone.

2.2.4. To determine the cost effectiveness of adding Rosiglitazone in treating uncontrolled type 2 diabetes mellitus with maximum combination of Sulphonylureas and Metformin.

CHAPTER THREE

CHAPTER THREE

METHODOLOGY

3.1 Study area

This study was carried out in Hospital University Science Malaysia (HUSM) which is a teaching hospital situated in Kubang Kerian, under Kota Bharu district. It functions as a tertiary referral centre for various disciplines and departments. This includes patients from the state of Kelantan and some parts of Terengganu. The study was approved by the Research and Ethics Committee, University Sains Malaysia.

3.2 Study design

The study was a randomized open label trial of optimal glycaemic control in patients on combination therapy with Rosiglitazone. The study was conducted between December 2004 until July 2005.

3.3 Source population

A total of 88 patients were selected, all of whom were on regular follow up at the diabetic clinic in hospital University Sains Malaysia, Kubang Kerian.

Inclusion and exclusion criteria

3.3.1 Inclusion criteria

1. Able to sign informed consent
2. Patients with type 2 diabetes mellitus
3. Age between 20 to 78 years old
4. BMI ≥ 23 and ≤ 40 kg/m2
5. Inadequate control of diabetes mellitus with HbA1c levels > 7.0 % and ≤ 12.0 %
6. On maximum dose of Glibenclamide (20 mg daily) or Gliclazide (320 mg daily) and Metformin (2000 mg daily) or Metformin SR (1700 mg daily)
7. Refused insulin therapy

3.3.2 Exclusion criteria

1. Use of other hypoglycaemic agents other than stable doses of Metformin/ Sulphonylureas or Thiazolidinediones within 8 weeks before screening
2. Renal dysfunction (serum creatinine level > 1.5 mg/dl for men or > 1.4 mg/dl for women
3. Abnormal liver function (serum ALT , AST or total bilirubin level > twice the upper limit of normal
4. Anaemia (Hb < 10 g % or hemoglobinopathies (thalasaemia) at start
5. Clinically substantial cardiac, respiratory, congestive cardiac failure or psychiatric illness.

3.4 Sampling frame

All patients with Type 2 diabetes mellitus receiving treatment at hospital USM, Kubang Kerian

3.5 Sampling method

Before randomization, a complete and thorough medical and social history was recorded from the patient. Exclusion study criteria were highlighted and inclusion study criteria were satisfied. Patients who fulfilled the inclusion criteria were given card numbers. The even numbers were recruited in the control group and the odd numbers were recruited in the treatment group. The control group was continued with maximum doses of sulphonylureas and metformin tablets. The treatment group was given rosiglitazone 4 mg once daily while maintaining the maximum dose of sulphonylureas and metformin.

3.6 Data collection

The data that were collected include:

a) demographic data

- age , sex, BMI

b) medical history

- duration of diabetes, complication of diabetes, treatment of diabetes

c) blood investigations

- HbA1c, FBS, Total cholesterol, HDL, LDL at baseline and at 24 weeks.

Data on blood investigation were repeated at 24 weeks.

d) drug cost

- the costs for metformin (1700 mg daily) or metformin (2000 gm daily) and glibenclamide (20 mg daily) or gliclazide (320 mg daily) in the control group and the adding cost of rosiglitazone (4 mg daily) were recorded at the first visit.

The information concerning the mode of treatment was obtained from the case notes as well as by interviewing the subjects.

Visits occur every 12 weeks for 24 weeks. Symptoms of side effects were asked in both groups on the second visit. Blood samples for the HbA1c were analyzed at the endocrine laboratory whereas plasma glucose and cholesterol were analyzed at the Chemical Pathology laboratory of Hospital University Sains Malaysia, Kubang Kerian. For blood glucose testing, 2.5 ml blood sample was collected in a Sodium Oxalate contained container. A glucose analyzer which uses the glucose oxidase was used for plasma glucose measurement. Blood samples for HbA1c measurement was collected in a plain container and analyzed using both the DiaSTATTM Hemoglobin A1c Analyzer (Bio- Rad Laboratories, USA) which is a low pressure liquid chromatography system (LPLC) and D10 Analyzer which is a high performance liquid chromatography (HPLC) , designed for the rapid and fully automated measurement of HbA1C. A comparison of DiaSTATTM and D10 gave correlation of 0.99. For TG and TC profile measurement, 2.5 ml blood sample was collected into EDTA contained container. The method used was Enzymatic method. The sample was analysed using Roche/ Hitachi analyser. The LDL cholesterol was by calculation (shown below)

In mmol/L :

LDL Cholesterol = Total Cholesterol – TG/ 2.2 – HDL Cholesterol (mmol/L)