COMPARISON OF SERUM FRUCTOSAMINE AND HbA1c AS AN INDEX OF POSTPRANDIAL GLYCAEMIC CONTROL IN DIABETIC PATIENTS

by

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LIST OF ABBREVIATIONS

BMI	:	body mass index
CAD	:	coronary artery disease
DCCT	:	Diabetes Control and Complications Trial
DECODE	:	Diabetes Epidemiology : Collaborative Analysis of Diagnostic Criteria in Europe
DM	:	diabetes mellitus
FPG	:	fasting plasma glucose
HbA1c	:	haemoglobin A1c
HDL	:	high density lipoprotein
IDDM	:	insulin dependent diabetes mellitus
IGT	:	impaired glucose tolerance
IPH	:	isolated postchallenge hyperglycaemia
LDL	:	low density lipoprotein
MBG	:	mean blood glucose
NIDDM	:	non-insulin dependent diabetes mellitus
OGTT	:	oral glucose tolerance test
PG	:	plasma glucose
PPG	:	postprandial plasma glucose
UKPDS	:	United Kingdom Prospective Diabetes Study

ABSTRACT

ABSTRAK

PERBANDINGAN DI ANTARA SERUM FRUKTOSAMIN DAN HbA1c SEBAGAI INDEKS KAWALAN PARAS GLUKOSA SELEPAS MAKAN BAGI PESAKIT DIABETES

Latarbelakang

Kawalan paras glukosa dalam darah selepas makan adalah penting untuk mengelakkan komplikasi mikro dan makrovaskular, mengurangkan rintangan terhadap fungsi insulin, memulihkan rembesan hormon insulin, dan mengelakkan komplikasi kepada bayi yang akan dilahirkan oleh wanita yang mengidap penyakit diabetes. Kedua-dua pendekatan rawatan iaitu; pengurangan paras glukosa semasa berpuasa dan pengurangan paras glukosa selepas makan adalah berperanan dalam strategi rawatan diabetes. Rawatan yang memberikan penekanan kepada pengawalan paras glukosa selepas makan dikaitkan dengan pengawalan paras glukosa secara keseluruhan yang lebih baik. Langkah ini mengurangkan kejadian komplikasi kronik pada individu yang mengalami masalah diabetes dan gangguan toleransi glukos. Oleh itu suatu kaedah ukuran yang dapat mencerminkan paras glukosa selepas makan yang jitu perlu digunakan.

Objektif

Objektif kajian ini adalah untuk menilai hubungan di antara serum fruktosamin dan HbA1c dengan paras glukosa selepas makan pada pesakit diabetes.

Kaedah kajian

Sejumlah 54 pesakit diabetes terlibat dalam kajian keratan rentas, prospektif ini. Semua pesakit telah diberikan diet piawai hospital untuk pesakit diabetes (sarapan dan makan tengahari). Profil paras glukosa (berpuasa, 2-jam selepas sarapan, sebelum makan tengahari dan 2-jam selepas makan tengahari) diambil pada hari yang sama. Perbezaan pada paras glukosa dalam plasma pada waktu-waktu tersebut dibandingkan dengan paras HbA1c dan fruktosamin yang diambil sekali pada masa berpuasa.

Keputusan

Dengan menggunakan analisa "multiple linear regression" dan mengambil faktor HbA1c sebagai variabel bersandar dan purata paras glukosa darah pada setiap masa sebagai variabel tidak bersandar, didapati hanya paras glukosa darah semasa berpuasa sahaja yang berkorelasi secara signifikan dengan HbA1c ($r=0.514$; $p=0.001$). Paras glukosa darah semasa berpuasa didapati mempunyai perkaitan yang baik dengan HbA1c bagi kumpulan tahap glukosa yang terkawal ($HbA1c \leq 7.0\%$)($r=0.459$; $p=0.007$) berbanding dengan kumpulan tahap glukosa tidak terkawal ($HbA1c > 7.0\%$)($r=-0.191$; $p=0.175$). Paras glukosa darah selepas makan mempunyai perkaitan yang lemah dengan HbA1c [paras glukosa 2 jam selepas sarapan: $r=0.254$ ($p=0.032$) dan paras glukosa 2 jam selepas makan tengahari: $r = 0.045$ ($p=0.375$)] begitu juga dengan fruktosamin [paras glukosa 2

jam selepas sarapan: r=0.245 (p=0.037) dan paras glukosa 2 jam selepas makan tengahari: r=0.146 (p=0.146)]. Prevalen "isolated postchallenge hyperglycaemia" adalah 46%, dengan majoriti (77%) adalah dari kalangan subjek yang mempunyai tahap kawalan glukosa darah yang terkawal. Terdapat perkaitan yang kuat di antara paras glukosa darah 2 jam selepas sarapan dengan paras glukosa sebelum makan tengahari (r=0.891; p=0.001).

Kesimpulan

Kedua-dua paras HbA1c dan serum fruktosamin didapati tidak mewakili purata paras glukosa selepas makan pada pesakit diabetes. Paras glukosa semasa berpuasa mempunyai perkaitan secara signifikan dengan HbA1c, oleh itu ia kekal sebagai kaedah utama bagi menentukan tahap kawalan menyeluruh glukosa darah. Oleh kerana HbA1c dan fruktosamin tidak menunjukkan perkaitan yang baik dengan paras glukosa selepas makan, kaedah-kaedah ukuran yang lain yang dapat mencerminkan paras glukosa selepas makan perlu dicari.

ABSTRACT

COMPARISON OF SERUM FRUCTOSAMINE AND HbA1c AS AN INDEX OF POSTPRANDIAL GLYCAEMIC CONTROL IN DIABETIC PATIENTS

Background

Postprandial glycaemic control is important in avoiding microvascular and macrovascular complications, lowering insulin resistance, restoring normal insulin secretion, and avoiding complications in the offsprings of women with diabetes. It is recommended that the treatment of diabetes include methods that lower both fasting and postprandial glucose levels. Treatment aimed at controlling postprandial glucose levels is always associated with better overall glucose control and thus may result in fewer chronic complications in individuals with diabetes and impaired glucose tolerance. In order to achieve good postprandial glycemic control, a proper monitoring tool that represents postprandial glycaemia status should be used.

Objective

To evaluate the relationship between fructosamine and HbA1c in assessing postprandial hyperglycaemia in diabetic subjects.

Research design and methodology

A total of 54 diabetic patients were included in this prospective, cross sectional study. All subjects were given a standard diabetic hospital diet (breakfast and lunch). Glycaemic profiles (fasting, 2-hours postbreakfast, prelunch and 2-hours postlunch plasma glucose) over the same day were obtained. The different time points plasma glucose (PG) was compared with measurement of HbA1c and fructosamine taken during fasting.

Results

In multiple linear regression analysis with HbA1c as dependent variable and mean blood glucose at each time points as independent variable, only FPG remained significantly correlated with HbA1c ($r=0.514$; $p=0.001$). FPG was well correlated with HbA1c in controlled glycemic group (HbA1c $\leq$ 7.0%) ($r=0.459$; $p=0.007$) but not in uncontrolled (HbA1c > 7.0%) group ($r=-0.191$; $p=0.175$). Postprandial blood glucose was poorly correlated with HbA1c [2-hours postbreakfast: $r= 0.254$ ($p=0.032$) and 2-hours postlunch: $r=0.045$ ($p=0.375$)] and serum fructosamine [2-hours postbreakfast: $r=0.245$ ($p=0.037$) and 2-hour postlunch: $r=0.146$ ($p=0.146$)]. The prevalence of isolated postchallenge hyperglycaemia in the study population was 46%, with majority (77%) of them within the controlled glycemic group. There was a strong correlation between 2-hours postbreakfast PG and prelunch PG ($r=0.891$; $p=0.001$).

Conclusion

Both HbA1c and serum fructosamine did not reflect mean postprandial blood glucose in our diabetic subjects. Fasting plasma glucose was significantly correlated with HbA1c and thus remained a good predictor of overall glycaemic control. Since both HbA1c and fructosamine did not correlate well with postprandial blood sugar, other markers of postprandial glycaemia need to be found.

CHAPTER ONE

CHAPTER 1

INTRODUCTION

Diabetes is a significant illness that is becoming prevalent in Malaysia and most parts of the world including both developed and developing countries. Numerous studies indicates that it is a major contributor to heart disease, stroke, end-stage renal disease, blindness, lower extremity amputation and significant impairment of nervous system. The main aims of therapy for diabetics are to relieve symptoms of hyperglycaemia or hypoglycaemia and to prevent the long-term complications from tissue damage (Table 1.1).

Table 1.1: The chronic complications of diabetes

Complication	Possible causes
Macroangiopathy (arteriosclerosis, myocardial disease)	Hyperglycaemia Hyperlipidemia Hyperinsulinemia Smoking ?Increased growth hormone level ?Platelet and other vascular factors
Microangiopathy (retinopathy, nephropathy, capillary basement membrane thickening)	Hyperglycaemia Protein (basement membrane) glycosylation Insulin deficiency
Neuropathy	Hyperglycaemia Sorbitol accumulation Deficient myoinositol Myelin glycosylation
Diabetic cataract	Hyperglycaemia Sorbitol accumulation Protein glycosylation
Collagen change	glycosylation

Adapted from Ledingham, J.G.G. and Warrell, D.A. (2000)

It has been shown that intensive insulin regimens to attain strict glycaemic control will slow down the development of microvascular complications in type 1 diabetic patients as well as in type 2 diabetic patients. Studies such as United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complication Trial (DCCT) have led to the conclusion that intensive glucose control with insulin or sulfonylureas markedly reduces the risk of microvascular complications (The UKPDS Group 1998; The DCCT Research Group 1993).

1.1 Effects of intensive versus conventional glycaemic control

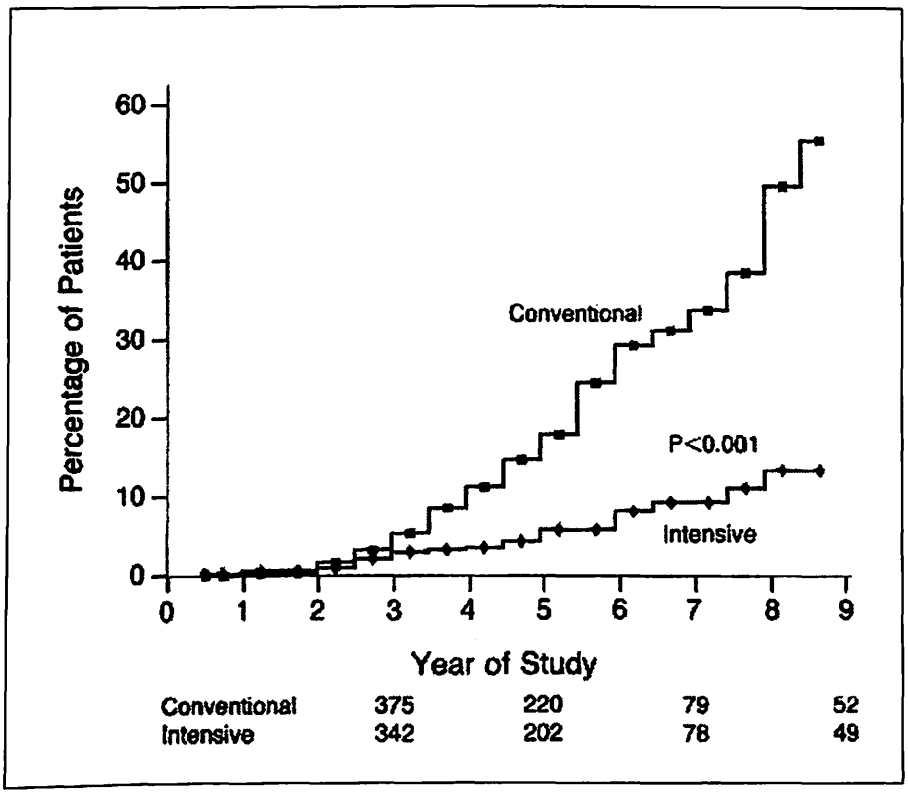
Herman (1999) in a systematic review assessing the impact of control of blood glucose in people with type 1 or type 2 diabetes concluded that intensive treatment compared with conventional treatment reduced the development and progression of microvascular complications.

1.1.1 Microvascular and neuropathic complications

Wang et al. (1993), before the publication of DCCT result, had conducted a systematic review of 16 small randomized controlled trials comparing intensive with conventional treatment in people with type 1 diabetes, with follow up ranging from 8 to 60 months. In the intensive therapy group, the risk of retinopathy progression was lower after more than two years therapy (odds ratio 0.49, 95% confidence interval 0.28-0.85; p=0.011). The risk

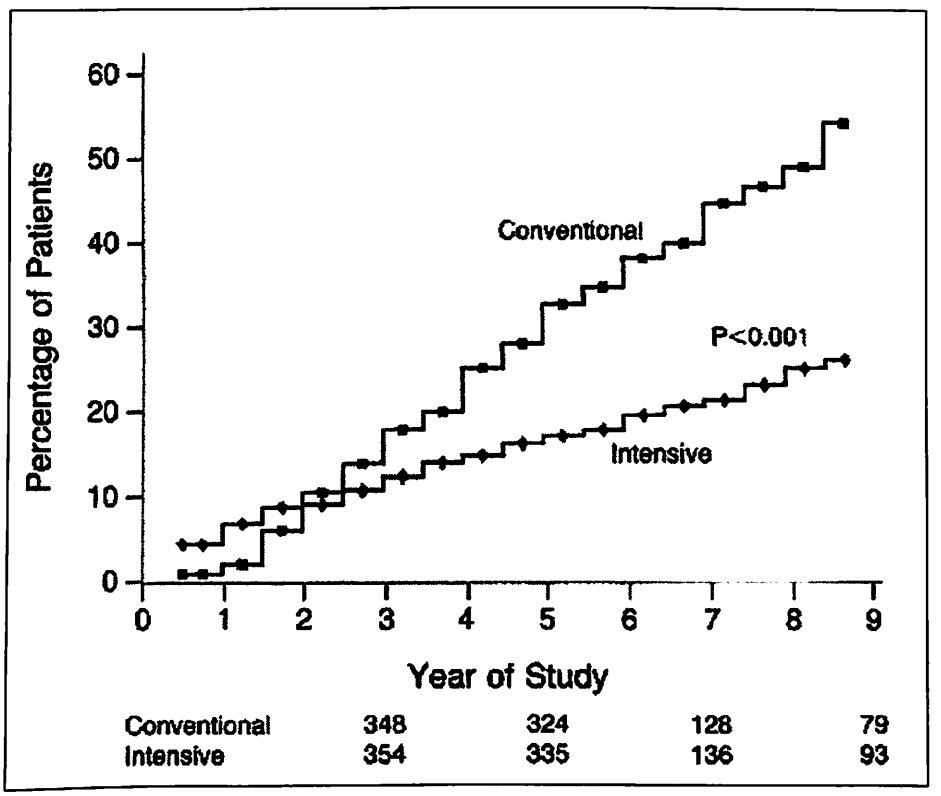
of nephropathy progression was also decreased significantly (odds ratio 0.34, 95% CI 0.20-0.58; $p<0.001$). Three subsequent longer term randomized controlled trials have repeated and extended these findings. The Diabetes Control and Complication Trial (DCCT) compared intensive with conventional treatment over 6.5 years in 1441 people with type 1 diabetes (The DCCT Research Group 1993). Patients were divided into two groups, 726 with no retinopathy at baseline (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) and were randomly assigned to intensive or conventional therapy. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76% (95% confidence interval, 0.62-0.85), as compared with conventional therapy (Figure 1.1). In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54% (95% confidence interval, 0.39-0.66) and reduced the development of proliferative or severe nonproliferative retinopathy by 47% (95 percent confidence interval, 0.14-0.67)(Figure 1.2).

The Kumamoto study compared intensive versus standard treatment in 110 people with insulin treated type 2 diabetes over six years (Ohkubo et al. 1995). The UKPDS is a 20-year, multicenter, prospective, randomized, interventional trial of 5102 newly diagnosed type 2 diabetes patients. The study compared intensive versus standard treatment. The relative risks of retinopathy, nephropathy and neuropathy were all reduced in all these studies.



Adapted from DCCT Research Group (1993)

Figure 1.1 **Cumulative incidence of a sustained change in retinopathy in patients with IDDM receiving intensive or conventional therapy in the primary-prevention cohort**



Adapted from DCCT Research Group (1993)

Figure 1.2 **Cumulative incidence of a sustained change in retinopathy in patients with IDDM receiving intensive or conventional therapy in the secondary-intervention cohort**

1.1.2 Macrovascular outcomes

In the Diabetes Control and Complications Trial, intensive treatment reduced the relative risk of any major macrovascular event from 0.8 to 0.5 events per 100 patient years (relative risk reduction 41%, 95% confidence interval 10% to 68%)(DCCT 1993). In the Kumamoto study, the number of major cerebrovascular, cardiovascular and peripheral vascular events in the intensive treatment group was half that of the conventional treatment group (0.6 versus 1.3 events per 100 patient years), but the event rates in this small trial were low and the results were not significant (Ohkubo et al. 1995).

The efficacy of these regimens (intensive glucose control) required an accurate method to estimate the degree to which this was achieved.

1.2 Monitoring glucose control

Blood and urine glucose testing and urine ketone testing has been used since long ago as they are easy, readily available and cheap. The tests could be done at home as part of self-monitoring program. They provided useful information for day-to-day management of diabetes. However, these tests could not provide the patient and health care team with a quantitative and reliable measure of glycaemia over an extended period of time.

There are five other useful measurements for defining diabetic control:

1) The mean blood glucose concentration (MBG)

MBG is measured in clinical trials by the mean of six daily values obtained before breakfast, mid-morning, before lunch, mid-afternoon, before dinner, and before sleep. Clinically, this has been replaced by the more simple measurement of HbA1c. In some cases, however, there was a disparity between the HbA1c values and MBG values based on the usual four times a day blood glucose measurements.

2) The degree to which blood glucose concentrations fluctuate within the same day can be formally measured as the mean amplitude of glycaemic excursions (MAGE) (Service et al. 1970).

3) The degree to which blood glucose concentrations fluctuate from day to day can be formally measured as the mean of daily differences (MODD) (Molnar et al. 1972).

4) HbA1c

The most widely used clinical test is measurement of blood glycated hemoglobin (also called hemoglobin A1c, glycohaemoglobin and glycosylated haemoglobin [HbA1c]). Hemoglobin A1c is a measure of the degree to which hemoglobin is glycosylated in erythrocytes and is expressed as a percentage of total hemoglobin concentration. It reflects the exposure of erythrocytes to glucose in an irreversible and time- and concentration-dependent manner. HbA1c levels provide an indication of the average

blood glucose concentration during the preceding 2–3 months, incorporating both pre- and postprandial glycaemia.

Hemoglobin formed in new red blood cells enters the circulation without any glucose attached. However, red cells are freely permeable to glucose. As a result, glucose becomes irreversibly attached to hemoglobin during the life of the red cell at a rate dependent upon the prevailing blood glucose. Several million red cells are destroyed every day, while an equal number of new ones are formed. Thus, the average amount of HbA1c changes in a dynamic way and reflects the mean blood glucose over the previous six to eight weeks (Nathan & Goldstein 1984). Because blood glucose concentrations vary widely during a 24-h period and from day to day in diabetes, the measurement of HbA1c is the most accepted indicator of long-term glycaemic control. However, the HbA1c level does not provide a measure of the magnitude or frequency of short-term fluctuations of blood glucose, which are particularly great in type 1 diabetes.

Several analyses have shown a strong correlation between HbA1c and MBG ($r \approx 0.81–0.95$), with each 1% change in HbA1c corresponding to a change in MBG of ≈ 35 mg/dl. This relationship was demonstrated in the Diabetes Control and Complications Trial (The DCCT Research Group 1987). A comparison was made between the mean blood glucose derived from seven measurements a day (before and 90 minutes after each of the three major meals, and before bedtime) and the HbA1c value in 278 patients with IDDM. A strong correlation was noted, such that a HbA1c value of 7 percent represents a MBG of about 150 mg/dL (8.3 mmol/L), and a HbA1c value of 9 percent represents a MBG about

210 mg/dL (11.7 mmol/L). DCCT also has shown that the HbA1c value can be referred to predict the risk for the development of many of the chronic complications in diabetes, analogous to using cholesterol determinations to predict the risk for development of cardiovascular disease. The American Diabetic Association (1995) has recommended that HbA1c testing should be performed routinely in all patients with diabetes, first to document the degree of glycaemic control at initial assessment, then as part of continuing care.

5) Fructosamine

Many proteins other than hemoglobin also undergo nonenzymatic glycation, leading to the formation of advanced glycosylation end products which may play a direct role in the development of diabetic microvascular complications. The plasma concentration of some of these proteins can also be used to estimate glycaemic control, and the term fructosamine has been applied to the ketoamines formed in this process (Armbruster 1987).

Several different methods are available for measuring plasma fructosamine (Armbruster 1987). Most (including colorimetric assays) are simpler, cheaper and more precise than assays for HbA1c. There is generally a good correlation between fructosamine and HbA1c values (Baker et al. 1985; Koskinen et al. 1987). Plasma fructosamine measurement is cheaper and easier, though it reflects shorter-term control compared to HbA1c, which is more expensive and technically difficult assay. Unlike HbA1c,

fructosamine has not yet been shown to be related to the risk of the development or progression of chronic complications of diabetes (American Diabetic Association 2000).

1.3 Postprandial blood glucose

Postprandial hyperglycaemia, or elevated mealtime glucose, is common in people with type 2 diabetes, yet often goes undetected. In an analysis by Erlinger et al. (2001), overall postprandial hyperglycaemia was present in 74% of those with diagnosed diabetes. While present in virtually all (99%) of diabetic adults under suboptimal glycaemic control (HbA1c $\geq$ 7.0%), it is also common (39%) among those under optimal control (HbA1c < 7.0%). Similar patterns were observed in those undiagnosed diabetes. Isolated postprandial hyperglycaemia (2 hours glucose $\geq$ 200 mg/dl and fasting glucose < 126 mg/dl) was present in 9.8% of adults with undiagnosed diabetes.

In the management of diabetes, health care providers usually assess glycaemic control with fasting plasma glucose (FPG) and premeal glucose measurements, as well as by measuring HbA1c. The goal in the management of patients with type 2 diabetes is to control fasting plasma glucose and glycosylated hemoglobin (HbA1c) levels. In patients with well-controlled diabetes (HbA1c <7%, or within 1% of normal) or glucose intolerance (fasting plasma glucose level <126 mg/dL, and a 2-hour plasma glucose of 140 to 200 mg/dL after 75 g of oral glucose), postprandial hyperglycaemia has a greater effect on HbA1c than fasting glucose levels. Jovanovic (1999) reported that the

postprandial glucose level at 1 hour is the best predictor of HbA1c in patients with well-controlled type 2 diabetes mellitus. In addition, a French study of patients with type 2 diabetes showed that glucose concentrations at 2 and 5 hours after a meal were better predictors of the HbA1c than prebreakfast or prelunch values (Avignon et al. 1997).

Patients spend a significant part of their day in the postprandial state. These mealtime/postprandial elevations contribute to overall blood glucose levels as measured by HbA1c. However, because diabetes management has traditionally focused on fasting plasma glucose levels (measurement of glucose in the absence of food), the surges in glucose that typically occur in type 2 diabetes patients after eating are often not evaluated. It is also noted that the postprandial glucose level is one of the most under-recognized and under-treated condition in diabetes.

1.4 The importance of glucose control

In the fasting state, the suppression of insulin production and stimulation of glucagon production control the concentration of blood glucose. These processes allow the liver to mobilize glucose from its glycogen stores and synthesize glucose from amino acids and pyruvate (gluconeogenesis). In addition, when insulin levels are low, the uptake of glucose by muscle is minimized, and adipocytes release free fatty acids. This homeostatic mechanism effects a stable plasma glucose level in the fasting state so that the brain, which has no energy stores, has a sufficient supply of nutrients for normal activity.

In the fed state, insulin is released in two phases. The first phase, a short, small burst released on food intake or an increase in plasma glucose concentration, preempts and decreases the postprandial glucose elevation. Later, a more sustained, second-phase insulin release directly proportional to the plasma glucose elevation occurs. In response to this biphasic release of insulin, the liver takes up glucose, converting it to glycogen (animal starch). The muscle and adipose tissues also take up glucose, storing it as glycogen and triglycerides, respectively. Furthermore, the production of free fatty acids in adipocytes is suppressed. The loss of first-phase insulin release has adverse metabolic and physiologic consequences, even if the second-phase release is adequate or even excessive.

1.4.1 First-phase insulin release

One of the earliest changes in the development of type 2 diabetes is the loss of first-phase insulin release, which occurs with fasting glucose levels of about 110 mg/dL. The loss can be documented by measuring plasma insulin concentrations over the 10 minutes immediately after an intravenous glucose load, calculated on the basis of the patient's weight. Lack of first-phase insulin release, an excellent predictor of both types of diabetes, is thought to be the earliest sign of the adverse effects of hyperglycaemia on insulin-producing β-cells and insulin-sensitive tissues (glucotoxicity) (Poitout & Robertson 1996). When the first-phase insulin response fails, plasma glucose levels rise sharply after a meal. Initially, this precipitates an increased stimulation of second-phase

insulin release that, in the early stages of glucose intolerance, may lead to postprandial hypoglycaemia resulting from elevated plasma insulin remaining after the nutrients have disappeared (Mitrakou et al. 1992). High insulin levels also cause downregulation of the insulin postreceptor pathways on the muscle and fat cells, thus increasing insulin resistance (Mandarino et al. 1984).

The higher glucose level in islet cells prompts a decrease in glucose-transporter activity, resulting in a reduction of insulin release (Rossetti et al. 1990), which is reversed by a decrease in plasma glucose level. If there is no decrease, the prolonged hyperglycaemia will eventually cause an accelerated loss of insulin-producing β-cells in both type 1 and type 2 diabetes (Poitout et al. 1996). Thus, metabolic loss of first-phase insulin release results in postprandial hyperglycaemia, an increase in insulin resistance, and a further decrease in insulin production.

The fasting blood glucose concentration is often used to monitor progress since it correlates well with HbA1c values (Howe-Davies et al. 1980). Fasting blood glucose concentrations are fairly stable in type 2 diabetic patients, but can vary by about 15 percent from day to day (Ollerton et al. 1999). Therapeutic goals for HbA1c and preprandial glucose levels have been established based on the results of controlled clinical trials. Unfortunately, the majority of patients with diabetes fail to achieve their glycaemic goals. It was noted that elevated postprandial glucose (PPG) concentrations may contribute to suboptimal glycaemic control (American Diabetic Association 2001).

An important role for postprandial glucose monitoring with therapy aimed at achieving postprandial glucose targets is suggested by teleologic argument, biochemical information, epidemiologic study and limited clinical data (Buse & Hroscikoski 1998).

Postprandial hyperglycaemia is also one of the earliest abnormalities of glucose homeostasis associated with type 2 diabetes and is markedly exaggerated in diabetic patients with fasting hyperglycaemia.

1.4.2 Effect of postprandial glucose levels on microvascular complications

The effects of postprandial hyperglycaemia on the development of microvascular complications of diabetes have been well documented. There is evidence that uncontrolled glycaemic peaks activate protein kinase C, the enzyme that may link hyperglycaemia to microvascular complications (Koya & King 1998). Elevated glucose levels lead to increased intracellular synthesis of diacylglycerol, which, in conjunction with elevated intracellular calcium, activates protein kinase C 939. The activity of protein kinase C impairs contraction of smooth muscle cells or pericytes, increases production of basement membrane materials, and enhances cell proliferation and capillary permeability. Thus, activation of protein kinase C by postprandial hyperglycaemia could be responsible for microvascular complications that may be developing even in the early stages of diabetes (Koya & King 1998).

Data from the National Health and Nutrition Examination Survey in 1998, showed that patients who had 2-hours postprandial glucose levels of 194 mg/dL had a threefold increase in the incidence of retinopathy, despite normal fasting glucose levels. Studies of Pima Indian and Egyptian populations revealed a similar increase in the incidence of retinopathy in subjects with normal fasting glucose levels but 2-hours postprandial glucose values of >200 mg/dL (American Diabetic Association 1997).

The development of microvascular complications in patients with type 2 diabetes has been documented in a number of clinical trials. In a long-term study of complications in patients who had type 2 diabetes for more than 25 years, Mohan et al. (1996), reported that postprandial glucose levels were associated with diabetic nephropathy. In a study of Pima Indian subjects, hyperfiltration, a precursor of diabetic nephropathy, in subjects with impaired glucose tolerance was found to increase with the onset of type 2 diabetes (Nelson et al. 1999). In a population study, Beghi et al. (1997) showed that elevated fasting and postprandial glucose levels, as well as prolonged disease duration, were associated with an increased incidence of diabetic neuropathy. Other studies which had shown that postprandial hyperglycaemia is associated with higher risk of microvascular complications includes studies performed by de Veciana et al.(1995), McCance et al.(1994) and Engelgau et al.(1997).

1.4.3 Postprandial glucose levels and macrovascular complications

The glycaemic threshold for the development of macrovascular complications is lower than that for microvascular complications, so there is more evidence for an association with postprandial glycaemia. Postprandial glucose elevations are associated with postprandial hyperinsulinemia and higher plasma levels of triglycerides, chylomicrons, chylomicron remnants and free fatty acids. In addition, high postprandial glucose levels result in protein and cellular glycosylation. Glycosylated LDL particles are more easily oxidized and taken up by macrophages through the scavenger receptor. This leads to higher foam cell production and ultimately, atherosclerotic plaque. In addition, glycosylated LDL also stimulates platelet aggregation. Glycosylated HDL is less efficient than nonglycosylated HDL in transporting cholesterol back to the liver for metabolism. Additionally, the formation of advanced glycosylated end products in the collagen of the vessel wall itself may directly stimulate or accelerate the atherosclerotic process (Bucala et al. 1995). Acute increases in plasma glucose also stimulate the production of free radicals, another factor involved in the atherosclerotic process (Habib et al. 1994). Excessive postprandial plasma glucose levels have also been associated with transient hypercoagulability resulting from increased thrombin production and decreased fibrinogen breakdown. These, in turn, result from the overproduction of plasminogen activator inhibitor, which directly inhibits tissue plasminogen activator activity. Control of postprandial hyperglycaemia reverses this hypercoagulable state (Ceriello et al. 1993).

The Honolulu Heart Study (Donahue et al. 1987) found that the risk of CAD correlated with plasma glucose levels measured 1 hour after a 50-g oral glucose load. The incidence

of CAD was twice as high in patients with postprandial plasma glucose levels between 157 and 189 mg/dL compared to those with levels <144 mg/dL, and the incidence of sudden death was doubled with postprandial plasma glucose levels >151 mg/dL. The Whitehall Study of British male civil servants showed that plasma glucose levels >96 mg/dL 2 hours after a meal were associated with a twofold increase in mortality from CAD (Fuller et al. 1980). Another British study, the Islington Diabetes Survey, reported that the incidence of major CAD (defined as major electrocardiographic changes or myocardial infarction) was 17% in subjects with a 2-hour postprandial glucose level between 120 and 180 mg/dL, compared with 9% in subjects with levels <120 mg/dL (Jackson et al. 1992). The Bedford Survey showed that protection from CAD was lost in patients with elevated postprandial glucose (Jarrett et al. 1982). By studying the progression of CAD in young men with previous myocardial infarction, Bavenholm et al. (1998) found that fasting and postprandial plasma glucose levels were independently related to disease progression. The Oslo Study indicated that the nonfasting plasma glucose level was a predictor of fatal stroke in diabetic patients, with the risk increasing by 13% for each 18-mg/dL elevation in postprandial glucose (Haheim et al. 1995). The Diabetes Intervention Study also showed that postprandial, not fasting, hyperglycaemia was an independent risk factor for myocardial infarction and cardiac death (Hanefeld et al. 1997). The risk of cardiovascular disease and all cause mortality increases with increasing postprandial blood glucose values (Lowe et al. 1997).

The Hoorn Study documented an increased risk of peripheral vascular disease in elderly patients with diabetes and in subjects with impaired glucose tolerance (Beks et al. 1995).

Ankle to brachial pressure indices < 0.9 were found in 7% of nondiabetic subjects, 9.5% of subjects with impaired glucose tolerance, 15.1% of patients with newly diagnosed diabetes, and 20.9% of patients with established type 2 diabetes. After logistical regression analysis and correction for other cardiovascular risk factors, the 2-hour postprandial plasma glucose value remained an independent risk factor for peripheral vascular disease, whereas plasma insulin did not (Beks et al. 1995).

Overexposure to insulin in response to postprandial hyperglycaemia has been shown to be a risk factor for cardiovascular events. The Paris Prospective Study found that postprandial hyperinsulinemia was a better predictor for fatal CAD than either hyperglycaemia or diabetes (Fontbonne et al. 1991). Similarly, the Helsinki Policemen Study revealed an independent association between fatal and nonfatal CAD events and 1- and 2-hour postprandial insulin levels that was stronger than that with fasting plasma insulin levels (Pyorala 1985). Finally, a report suggested an association between increase in postprandial levels of insulin and decrease in cognitive function in women aged 55 years and over (age adjusted regression coefficient -0.10 per 50 mU/l insulin; 95% CI -0.16 to -0.04)(Stolk et al. 1997).

Another factor associated with postprandial hyperglycaemia is postprandial hyperlipidemia. Elevated triglyceride levels after a meal predict the development of CAD and are associated with carotid artery atherosclerosis in nonobese white subjects (Sharrett et al. 1995). Therefore, a reduction of postprandial glucose levels, which also reduces plasma insulin and lipids after a meal, could reduce the incidence of CAD.

The European DECODE study also found that an elevated postprandial glucose level was a significantly better predictor of risk of death than the fasting plasma glucose level (DECODE 1999).

1.4.4 Postprandial glucose levels and pregnancy outcomes

The effect of postprandial hyperglycaemia was also demonstrated in pregnant women in studies by Jovanovic-Peterson et al. (1991). They reported that in pregnant patients with diabetes, postprandial hyperglycaemia is more closely related to fetal macrosomia than preprandial hyperglycaemia in pregnancies complicated by preexisting diabetes. That observation led to recommendations for both preprandial and postprandial blood glucose monitoring in women with gestational diabetes (Jovanovic 1995). Similarly, Combs et al. (1992), reported that there was a strong correlation between macrosomia and high postprandial glucose levels occurring during the 29th to 32nd week of pregnancy.

In a trial reported by de Veciana et al. (1995), of 66 gestational diabetic women who monitored either preprandial or postprandial blood glucose levels, the final HbA1c level was significantly lower in women who used postprandial monitoring. Moreover, the rate of cesarean-section and the number of large-for-gestational-age infants were significantly lower in women who used postprandial monitoring to achieve improved HbA1c level.

Demarini et al. (1994) studied two groups of pregnant women with different target levels of postprandial glucose, <120 and <140 mg/dL, respectively. Neonatal hypoglycaemia

occurred at a higher frequency in babies born to women in the <140 mg/dL group. Because of these studies, the American Diabetes Association now recommends monitoring both fasting and 1-hour plasma serum glucose levels during pregnancy (Jovanovic 1995).

1.5 Methods of controlling postprandial hyperglycaemia

Postprandial glycaemic control is important in avoiding microvascular and macrovascular complications, lowering insulin resistance, restoring normal insulin secretion and avoiding complications in the offspring of women with diabetes. It is recommended that the treatment of diabetes include methods that lower both fasting and postprandial glucose levels.

Strategies for the management of diabetes have evolved considerably over the last few years. We have moved from an era where glycaemic control was aimed primarily at avoiding the symptoms associated with hyperglycaemia (polyuria, polydipsia, weight loss and fatigue) to an era where the primary objective is to attain near normal glycaemic control in an effort to prevent or delay the microvascular and macrovascular complications of diabetes. This switch in emphasis, and the parallel developments in pharmacologic agents and lifestyle intervention techniques, translates into greater attention to glycaemic control in the postprandial state. Therefore, therapies that focus on lowering postprandial glucose are beneficial and also important in reducing diabetic complications and mortality and currently an important focus for therapy.

These had led to the development of newer oral hypoglycaemic agents or insulin with the target of controlling postprandial hyperglycaemia. In type I diabetes, postprandial glucose levels can be controlled only with very fast-acting insulin, such as insulin lispro (Feinglos et al. 1997; Holleman & Hoekstra 1997) and also insulin aspart (Home et al. 1998). New antidiabetic drugs in development, such as the injectable amylin analog pramlintide and glucagon-like insulinotropic polypeptide (GLIP), target the suppression of postprandial hyperglycaemia (Joubert et al. 1990; Schmitz et al. 1997). These drugs slow gastric emptying and suppress glucagon production. In patients with type 2 diabetes who require none or just one evening or nighttime injection of intermediate-acting insulin to control the fasting glucose level, an oral agent capable of stimulating an insulin release sufficient to cover the meal or delay the absorption of glucose from the intestine (bolus agents) should be used. Drugs with these properties should be used in combination with oral agents that lower insulin resistance, decrease hepatic glucose production, or stimulate insulin production (basal agents). This therapy can be described as oral basal-bolus therapy for type 2 diabetes, in contrast to injection-based basal-bolus therapy using insulin for type 1. Among other available agents, the alpha glucosidase inhibitors, with acarbose serving as the prototype, specifically reduces insulin requirements. Not coincidentally, acarbose's primary hypoglycaemic effect is on postprandial glucose levels. By altering the postprandial rise in glucose, acarbose spares the amount of insulin needed.

Bolus drugs include acarbose, miglitol, repaglinide, and possibly glimepiride. Examples of basal drugs are troglitazone, pioglitazone, rosiglitazone, metformin, long-acting

sulfonylureas, and intermediate and long-acting insulins. It is easier to achieve the long-term HbA1c goal $\leq$ 7% using basal-bolus therapy, because at this level of control, the biggest contributor to HbA_{1c} values is the postprandial glucose level (Jovanovic 1999).

1.6 Relationship between postprandial blood glucose with HbA1c and fructosamine

Regardless of the drugs available, for optimal postprandial glycaemic control, patients must monitor their glucose levels after eating a meal. When diabetes is poorly controlled, only preprandial glucose readings are necessary. However, once control is achieved, it is important to monitor glucose levels both before and after meals. This allows for appropriate adjustments of bolus drug administration to reach postprandial glycaemic goals and to maximize the patient's protection from diabetic complications.

The relative contributions of FPG and PPG to HbA_{1c} have been studied only recently. In general, fasting plasma glucose, postprandial blood glucose, and especially mean blood glucose (MBG) concentrations, defined by the average of multiple measurements of glucose taken throughout the day, are highly correlated with HbA_{1c}. FPG has been correlated with overall glucose control, as measured by HbA1c (Graf 1978; McCance 1988).

So far, the method commonly used (HbA1c and serum fructosamine) is validated only for monitoring of mean blood glucose (MBG) and fasting blood glucose (Howe-Davies et al.

1980). In Malaysia, the measurement of glycated albumin (fructosamine), which is substantially cheaper than HbA1c has not been widely adopted. It is only done for monitoring gestational diabetes.

It has long been accepted that the 'gold standard' marker of overall glycaemic control in diabetes mellitus is the level of glycated haemoglobin (HbA1c). It is the preferred marker for glycaemic control compared to fructosamine. It is, however, an expensive and not readily available in certain hospitals in this region. Plasma fructosamine measurement is cheaper and easier, and also it reflects shorter-term glycaemia. Furthermore, diabetic patients can be monitored more closely and frequently in diabetic clinics, rather than every 3 months or so. However, trials only focused on fasting or premeal blood glucose rather than postprandial blood glucose. For these reasons this study has been designed to evaluate the relationship of HbA1c and serum fructosamine as an index of postprandial glycaemic control.

CHAPTER TWO

CHAPTER TWO

OBJECTIVES

2.1. General objective

To evaluate the relationship between fructosamine and HbA1c as a predictor of postprandial hyperglycaemia in diabetic subjects.

2.2. Specific objectives

1) To determine the frequency of subjects with normal FPG but with abnormal postprandial blood glucose (isolated postchallenge hyperglycaemia)
2) To compare the correlation between fructosamine and HbA1c with postprandial hyperglycaemia
3) To evaluate the relationship between postprandial plasma glucose with other time point plasma glucose
4) To evaluate the differences of plasma glucose between the controlled and uncontrolled glycaemic groups