THE PREVALENCE AND RISK FACTORS OF COGNITIVE DYSFUNCTION IN PATIENTS WITH DIABETES MELLITUS IN IRAQ

by

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LIST OF ABBREVIATION

Aβ42	Amyloid Beta peptide 42
ACCORD-MIND	Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes
ACEI	Angiotensin Converting Enzyme Inhibitors
AD	Alzheimer's disease
ADA	American Diabetes Association
ADL	Activities of Daily Living
AGES-Reykjavik	Gene/Environment Susceptibility–Reykjavik
ANOVA	Analysis Of Variance
ARBs	Angiotensin II-Receptor Blockers
ATP	Adinosine triphosphate
BMI	Body Mass Index
CASCADE	The Cardiovascular Determinants of Dementia
CD	Cognitive Dysfunction
CDT	Clock Drawing Test
CIB	Clock-in-a-Box test
CIND	Cognitive Impairment No Dementia
CSF	Cerebrospinal Fluid
CMS	Center of Medicare and Medicaid Services
CNS	Central Nervous System
CT	Computed Tomography
CVA	Cerebrovascular accident
CVD	Cardiovascular diseases
DBP	Diastolic Blood Pressure
DCCT	The Diabetic Control and Complications Trial Research Group
DECODE	Collaborative Analysis of Diagnostic Criteria in Europe
DM	Diabetes Mellitus
DSST	Digit Symbol Substitution Test

DWMHs	Deep White Matter Hyperintensities
DWMLs	Deep White Matter Lesions
EDIC	Epidemiology of Diabetes Interventions and Complications
EC	Entorhinal Cortex
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FLAIR	Fluid Attenuation Inversion Recovery
FOV	Field Of View
FPG	Fasting Plasma Glucose
GDS	Geriatric Depression Scale
HAAS	Honolulu-Asia Aging Study
HbA1C	Glycosylated Hemoglobin
HDL	High Density Lipoprotein
HDS	Hiv Dementia Scale
HEPESE	Hispanic Established Population for the Epidemiological Study of the Elderly
IADL	Instrumental Activities of Daily Living
IDE	Insulin-Degrading Enzyme
IHD	Ischemic Heart Disease
LDL	Low Density Lipoprotein
MCI	Mild Cognitive Impairment
MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MTA	Medial Temporal Lobe Atrophy
NCF	Normal Cognitive Function
NDDG	National Diabetes Data Group
NFTs	Neurofibrillary Tangles
NICE	National Institute Of Clinical Excellence
NPH	Neutral Protamine Hagedorn or Isophane
NPL	Neutral Protamin Lispro
PET	Positron emission tomography

PMD	Persatuan Diabetes Malaysia
PVH	Periventricular Hyperintensities
PWMLs	Periventricular White Mater Lesions
RAS	Renin-Angiotensin System
RAVLT	Rey Auditory Verbal Learning Test
RBC	Red Blood Cell
RT	Repetition Time
SAE	Subcortical Arteriosclerotic Encephalopathy
SBP	Systolic Blood Pressure
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
SPWMLs	Small Punctuate White-Matter Lesions
Syst-EUR	Systolic Hypertension in Europe
TE	Time to Echo
TGs	Triglycerides
TICS	Telephone Interview for Cognitive Status
TZD	Thiazolidenidiones
UDES	Utrecht Diabetic Encephalopathy Study
UKDPS	United Kingdom Prospective Diabetes Study
VBM	Voxel-Based Morphometry
VLDL	Very Low Density Lipoprotein
WASI	Wechsler Abbreviated Scale of Intelligence
WHO	World Health Organization
WMH	White Matter Hyperintesities

PREVALENS DAN FAKTOR RISIKO DISFUNKSI KOGNITIF DALAM KALANGAN PESAKIT DIABETES MELITUS DI IRAQ

ABSTRAK

Diabetes melitus merupakan suatu penyakit metabolik kronik yang terkenal berdasarkan komplikasinya yang banyak.Ia merupakan penyakit yang boleh diurus sendiri atau swaurus (self-managed disease), yang memerlukan kognisi intak untuk mengekalkan kualiti hidup yang baik. Disfungsi kognitif adalah perubahan neurodegeneratif yang boleh dikaitkan dengan diabetes melitus.Ia dianggap sebagai tahap pertama penyakit dementia dan Alzheimer, yang bersama-sama dengan diabetes merupakan masalah kesihatan prevalens global yang semakin. Kajian ini mengkaj perkaitan yang tidak jelas antara diabetes melitus dan disfungsi kognitif.Kajian ini berurusan dengan prevalens disfungsi kognitif dalam kalangan diabetes.Ia juga turut membandingkan insidens atau keberlakuan gangguan kognitif (cognitive impairment) dalam diabetes jenis 1 dan 2. Disamping itu, turut dikaji pengaruh diabetes sebagai suatu penyakit kronik, komplikasinya, serta rawatan terhadap prestasi kognitif.Suatu metodologi kawalan rentas - kes digunakan dalam usaha mengekalkan objektif kajian.Dua jenis peralatan digunakan untuk menilai disfungsi kognitif, iaitu Pemeriksaan Status Miniminda (Mini-Mental Status Examination, MMSE), dan Penilaian Kognitif Montreal (Montreal Cognitive Assessment, MoCA). Selepas mengira saiz sampel, seramai 380 orang pesakit diabetes, dan 100 orang subjek kawalan yang memenuhi kriteria yang ditetapkan terlibat dalam kajian ini.Sebagai suatu subkajian, perkaitan antara status penanda pengimejan resonans magnet (magnetic resonance imaging, MRI) otak dan prestasi

kognitif dinilai bagi sebilangan peserta yang tertentu. Dapatan kajian menunjukkan bahawa berdasarkan penggunaan MMSE, prevalens disfungsi kognitif adalah 16.3% bagi pesakit diabetes, dan 7% bagi subjek kawalan. Berdasarkan penggunaan MoCA, prevalens disfungsi kognitif adalah 59.2% bagi pesakit diabetes, dan 15% bagi subjek kawalan. Dari segi jenis diabetes, tiada perbezaan signifikan ditemui antara prestasi kognitif jenis 1 dan 2.Bagi pesakit diabetes, disfungsi kognitif adalah berkaitan dengan glisemia yang tidak terkawal, yang diwakili oleh tahap HbAIC yang tinggi.Ia juga dikaitkan dengan obesiti (kegemukan) dan kurang senaman serta penggunaan suplemen. Dalam kedua-dua kes (MMSE dan MoCA), prestasi kognitif yang buruk dikaitkan dengan pesakit yang diberi sulfonilurea bersama-sama dengan insulin, prestasi yang baik adalah dalam kalangan pesakit yang menggunakan amaryl®, monoterapi insulin atau terapi daripada gabungan metformin-insulin.Akhir sekali, terdapat perkaitan yang signifikan di antara disfungsi kognitif dan isyarat hiperintesiti yang tidak normal dalam otak.Sebagai kesimpulan, disfungsi kognitif mungkin merupakan antara komplikasi diabetes melitus. Justeru, ia sepatutnya diberi pertimbangan sewajarnya sebagai suatu keadaan yang memerlukan penilaian klinikal serta pelan terapeutik.

THE PREVALENCE AND RISK FACTORS OF COGNITIVE DYSFUNCTION AMONG PATIENTS WITH DIABETES MELLITUS IN IRAQ

ABSTRACT

Diabetes mellitus is a chronic metabolic disease that is distinguished by many complications. It is mainly a self-managed disease that needs intact cognition to maintain better quality of life. Cognitive dysfunction is a neurodegenerative changes that might be associated with diabetes mellitus. It is considered as the first stage of dementia and Alzheimer disease which is together with diabetes are global growing prevalence health concerns. This study investigates the unclear relationship between diabetes mellitus and cognitive dysfunction. It deals with occurrence of cognitive dysfunction among diabetes. It also compares the occurrenceof cognitive impairment in type 1 and type 2 diabetes. In addition, it investigates the influence of diabetes as a chronic disease, its complication and treatment on cognitive performance. A comparative cross-sectional methodology was adopted to achieve the study objectives. Two tools were used to evaluate cognitive dysfunction, the Mini-Mental Status Examination (MMSE), and Montreal Cognitive Assessment (MoCA). After calculating sample size, 380 patients with diabetes, and 100 control subjects who met inclusion and exclusion criteria were included in the study. As a sub-study, the association between brain magnetic resonance imaging (MRI) marker status and cognitive performance was assessed for certain number of participants (n=10 per arm). The major findings of this study are that according to MMSE, the prevalence of cognitive dysfunction was 16.3% of patients with diabetes and 7% of controls. By using MoCA, cognitive dysfunction prevalence was 59.2% of patients with diabetes,

and 15% of controls. In terms of diabetes types, no significant difference was found between the cognitive performance of type 1 diabetes and that of type 2 diabetes. In patients with diabetes, cognitive dysfunction was associated with uncontrolled glycemia represented by high levels of HbA1c. It is also associated with obesity and lack of exercise and supplements use. In both, MMSE and MoCA cases, the worse cognitive performance was associated with patients on sulfonylurea in combination with insulin, and the best performance was among patients who usedglimepiride (amaryl®), insulin monotherapy or metformin-insulin combination therapy. Finally, there was a significant association between cognitive dysfunction and abnormal signal hyperintensities in the brain. In conclusion; cognitive dysfunction might be among diabetes mellitus complications list. It should be given consideration as a condition that needs to be part of the clinical assessment and the therapeutic plan of diabetes mellitus.

CHAPTER ONE
INTRODUCTION

1.1 Overview

Diabetes mellitus is a widespread metabolic abnormalities and is characterized by hyperglycemia (high blood glucose levels) resulting from discrepancy in insulin secretion (type 1 diabetes), resistance to insulin associated with an inadequate secretion of insulin, or both (type 2 diabetes) ("Report of the expert committee on the diagnosis and classification of diabetes mellitus," 2003).

During the last decade, studieshave demonstrated that diabetesmellitus might be classified to different kinds with various etiologies, althoughpathological progressionmight be comparable after the disease onset (Koda- Kimble, Young, Kradjan, &Guglielmo, 2005). Type 1 diabetes is caused by the obliteration of beta-cells in pancreas. This leads to complete insulindeficiency which is known as insulin–dependent diabetes mellitus (IDDM). Most commonly, type 1 diabetes involveswith subjectsnear puberty (Koda- Kimble *et al.*, 2005). Type 1 diabetes is treated by injection of insulin to replace absent endogenous form of insulin, diet and exercise (Koda- Kimble *et al.*, 2005).

The other type is type 2 diabetes, a non-insulin-dependent diabetes mellitus (NIDDM). This typeoccurs when the pancreas retains part ofpancreaticbeta-cell role, but the inconsistentrelease of insulin is inadequate to preserve glucose homeostasis. The onset of this type of diabetes is in the adulthood(Howlett, Porte, Allavoine, Kuhn, & Nicholson, 2003). Factorsthat affect type 2diabetes development areobesity, hereditaryrisk factors,environmental aspect, physical activity, overweight birth and gestational diabetes(ADA, 2010).Non-insulin dependentdiabetes is managed by diet,

exercise and oral anti-diabetic agents.Insulin is used to treat diabetes type 2when the oral treatments fail to maintain glycemiccontrol (Stenman, Melander, Groop, & Groop, 1993). Oral diabetes treatment that are used in type 2diabetes include: Sulfonylurea; biguanides; α-glucosidase inhibitors;thiazolidenidiones and non-sulfonylurea insulin secretogogues (Stenman *et al.*, 1993).Type 1 diabetesconsists 5-10% of diabetes population, while type 2 accounts for 90-95%. The diabetes prevalence among adults was found to be 2.8% in 2000 and is estimated to beincreased to 4.4% by the year 2030 worldwide(Wild, Roglic, Green, Sicree, & King, 2004).

Bothtypes of diabetes have prognosisof numerous micro- and macro-vascular complications, such as retinopathy, nephropathy, peripheral neuropathy, dyslipidemia and cardiovascular events. The clinical signs and symptoms in addition to the diagnostic methods ofaforementioned complications are established thoroughly (ADA, 2005). The development of this chronic disease complications is relianton the diabetes duration and the level of metabolic control(ADA, 2002).

Type 2 is commonly undiagnosed for many years because the symptoms at the beginning are not severe enough to provoke evident diabetes symptoms. About half of diabetes population may be undiagnosed(ADA, 2005). Yet, such cases are at high incidence of showing diabetes complications and other related disorder. Moreover, type 2 is a slow onset disorder starting from normal glucose homeostasis, borderline hyperglycemia to diabetes(ADA, 2006). Borderline diabetes often develops to full-blown diabetes with increased complications risks (ADA, 2006).

Cognitive function is the term used to explainindividual's state of memory, attention span and consciousness (including alertness and orientation). Cognitive

functioning had been the subject of many studies in both types of diabetes(Kodl & Seaquist, 2008; Munshi *et al.*, 2006). Several cross-sectional and case-control researches since 1980s revealed positive associations between diabetes and cognitive impairment (Gregg & Brown, 2003).

1.2 Pathophysiology of Diabetes Mellitus:

Insulin is considered as amain anabolic hormone thathas a vitaleffect to maintaingrowth and the development of tissues. Endogenously, insulin is released by the pancreatic β-cell to maintain homeostasis. This biological event take place as aresponse toincreased level of circulating glucose and amino acids after food ingestion(Moller & Jorgensen, 2009). Insulin regulates circulating glucose level at many parts of the body. It reduces hepatic production of glucose bygluconeogenesis and glycogenolysis. It also increases the rate of glucose uptake particularly into skeletal muscles andfatty tissues(Shulman, 2000). Insulin increaseslipogenesis in liver and adipocytes, and decreasesthe release of fatty acid fromadipose tissue (Sesti, 2006). During fasting, hyperglycemia is caused by abundant basal hepatic glucose production as a result of liver resistance to insulin action. Hyperglycemia resulting from food ingestion is caused by the dysfunction ofβ-cell in the pancreas (insufficient insulin production), hepatic glucose over production and lack of glucose uptake by peripheral tissues(Giorgino, Laviola, & Leonardini, 2005).

Chronic hyperglycemia affects the secretion kineticsfrom the β-cell by time. Consequently, tissue sensitivity to insulin will beaffected (glucotoxicity)(Dailey, 2004). Thus, both impaired insulin action and dysfunctional insulin secretionexplaintype 2 diabetes pathogenesis (Giorgino *et al.*, 2005). In PimaIndians (Bogardus, 1993) and Mexican Americans (Gulli, Ferrannini, Stern, Haffner, &

DeFronzo, 1992), insulinresistance is the primaryexclusive cause. On the other hand,β-cell deficiency inwhite populations was the most marked cause during early stage diabetesmellitus development (Vaag, Henriksen, Madsbad, Holm, & Beck-Nielsen, 1995).

1.3 Treatment

The most important point in treating hyperglycemia in patients with diabetes isto prevent or delay the development of complications of this disease that exist as a threatto the quality of life. Three major components to treat type 2 diabetes include: diet, pharmacologic therapy (oral hypoglycemicagents, and insulin) and exercise. Type 1 diabetes is managed by insulin, diet and increasing physical activity.

1.3.1 Diet

The cornerstone of diabetes management is diet and exercise. These two diabetes managing ways should be adopted as a first step of diabetes type 2 therapeutic plan (ADA, 2010). However, benefits from these interventionsare inadequate for nearly all patients with type 2 diabetes (Consoli *et al.*, 2004).

1.3.2 Pharmacologic therapy

Treatment of diabetes type 1 is insulin plus diet and exercise. Only sulfonylureas as well as insulin exist to treat diabetes type 2 untilmid-1990s.Later, metformin, α-glucosidase inhibitors, thiazolidenidiones andnon-sulfonylureas were introduced to the markets after being approved by the FDA (Food and DrugAdministration). Many compoundsof various mechanism of actionare under research(Koda- Kimble *et al.*, 2005). Usually, diabetes type 2patients are prescribed other agentsto managetheir diabetes-associated complications such ashypertension, cardiovascular events, dyslipidemia,and other chronic illnesses that that may be causedby aging. From this

point,it could be said that diabetes type 2treatment should be the simplest, most effective, and the safestregimen that treat diabetes and its complicationsproperly (ADA, 2008).

1.3.2(a)α-Glucosidase inhibitors

The only member belongs to this group is acarbose 25, 50and 100mg and miglitol. Theydo not lead toincreasedbody weight(Hong, Xun, & Wutong, 2007). The adverse effects that might be caused by this group are diarrhea and bloating. Starting with lowest doses and increase it gradually on needis helpful to avoid diarrhea (ADA, 2006). The mechanism of action of this group is toinhibitcarbohydrates digestion that leads todecrease the absorption of glucose (Hong *et al.*, 2007).

1.3.2(b)Non-sulfonylurea insulin secretagogues

Repaglinide, and nateglinide, are members of insulin secretion-stimulating group. It acts by helping the pancreas produce insulin (Culy & Jarvis, 2001). Repaglinide was approved by FDA of United States of America in 1997. The other member wasapproved in 2000(Culy & Jarvis, 2001). The intake recommendation of usage of this group is to take the doseprior meals immediately and to skip the dose whenever the meals is skipped(ADA, 2006).

1.3.2(c)Sulfonylureas

Several members of sulfonylureas have been discovered.Members of the first generation are: chlorpropamide, Acetohexamide, tolbutamide, and tolazamide (ADA, 2006). The secondgeneration includes glipizide and glyburide. The third generation is represented by Glimipride which was approved in 1997. One of the major adverse effects of sulfonylureas is hypoglycemia when insulin production overshoots.This adverse effect is found to be lesserassociated with this group compared to insulin

(Patlak, 2002). All members have common mechanism of action by stimulating the production of insulin by Potassium ATP channel inhibition. Although,each memberhave different pharmacokinetics and side effects (Zimmerman, 1997).

1.3.2(d)Thiazolidenidiones (TZDs)

Rosiglitazone and pioglitazone received the FDA of the United States approval was in 1999, troglitazone which was approvedin 1997 which has been withdrawnfrom markets in 2000 due toitseffect of hepatotoxicity effect(Mudaliar & Henry, 2001). This group acts by increasingthe utilization of glucose in adipose tissues and skeletal muscles. In addition, it decreasesthe hepaticproduction of glucose. This group also increasesthe uptake of fatty acid and reduces lipolysis inthe adipose tissue.Eventually, these events leads to reduction of postprandial and fasting plasma glucose, andinsulin (Olefsky, 2000). Patients with liver dysfunction andmajorcardiac diseases have contraindications to this group (O'Moore-Sullivan & Prins, 2002). Most patients on TZDs will requirecombination therapy with other anti-diabetic treatment to achievethe desired long term glycemic control (Turner, Cull, Frighi, & Holman, 1999).

1.3.2(e)Metformin

Phenformin, the first discovered member of biguanide, was available in 1977. Its association with lactic acidosis was the major reason for it to be withdrawn from the markets (Koda- Kimble *et al.*, 2005). The only licensed member of biguanide until now is metformin (Koda- Kimble *et al.*, 2005). Fortunately, metforminis not associated withhypoglycemia as an adverse effect as with sulfonylureas. In addition, it is prescribed to overweight patients (with body mass index > 25kg/m^2) as it does notpromote weight gain and it does stimulate the secretion of insulin from pancreas

(Kimmel & Inzucchi, 2005). Itreduces the hepatic glucose production which will lead todecrease fasting plasma glucose level (Hundal *et al.*, 2000).Metformin also increases the muscle tissue sensitivity to insulin that helps to decrease blood glucose concentration. Metformin is contraindicated in conditions such as renal dysfunction, liver impairment, pregnancy, stress conditions and other acute illnesses("Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)," 2008)

1.3.2(f)Insulin

Exogenous insulin is mandatory for patient with diabetes type1survivaldue to the almost complete destruction ofpancreatic β-cells. It also hasa majorpart in treating subjects withdiabetes type 2when oral anti-diabetic fails to achieve the therapeutic goal(Mayfield & White, 2004). Acute illnesses, surgical operations, pregnancy and breast feeding, glucose toxicity and other metabolic disorders are conditions (such as diabetic ketoacidosis, lactic acidosis and hyperosmolar non-ketotic coma) that indicate insulin use. Another insulin indication is the presence of contraindicationsto oral anti-diabetic among diabetes type 2 patients(Mayfield & White, 2004; Ministry of Health, 2004).One study found that 27% of diabetestype2are using insulin (Koro, Bowlin, Bourgeois, & Fedder, 2004).

Exogenous insulin isfound withdifferent pharmacokinetics, pharmacodynamics,as well asphysical and chemical properties(Koda- Kimble *et al.*, 2005).Parenterally administered insulin forms are, rapid-acting insulin analogs solution,short-acting (regular), intermediate-acting and long-acting (Ultra lente, and insulin glargin) for subcutaneous injection (Bolli & Owens, 2000). Other types of insulin is the pre-mixed insulin which is aprecise mixture of intermediate-acting and short-acting insulin in one vial or insulin pen (Koro *et al.*, 2004).Glycemic control improvement

was observed when insulin used in combination with oral anti-diabetic agents among patients who failed to achieve glycemic control even by using theupper limit combination of oral anti-diabetic drugs (Pugh *et al.*, 1992). It can be used as combination with metformin (Ponssen, Elte, Lehert, Schouten, & Bets, 2000), sulfonylureas(Wright, Burden, Paisey, Cull, & Holman, 2002), thiazolidenidiones (TZDs) (Coniff, Shapiro, Seaton, Hoogwerf, & Hunt, 1995; Derosa *et al.*, 2004), and α-glucosidase inhibitors (Coniff *et al.*, 1995).

1.4 Complications of diabetes

Diabetes is a predisposing factor for many co-morbid complications, and mortality in patient with diabetes(Cusick *et al.*, 2005). It has been found that diabetes islisted as the sixth cause of mortalityin the United State (> 71,000 deaths per year)(Center of Medicare and Medicayd Services (CMS) Public Affairs Office, 2004). The DiabetesEpidemiology: Collaborative Analysis of Diagnostic Criteria in Europe(DECODE) study group (1999) found that diabetesdoublethe mortality risk over 10 years of follow-up compared with non-diabeticcontrols(DECODE, 1999; Stancoven & McGuire, 2007).

Diabetic complications are of two types.Acute complications which include hypoglycemia and hyperglycemia, while the other type is the chronic complications that are subdivided into two types, macrovascular and microvascular complications. Microvascular complications includeretinopathy, neuropathy, and nephropathy, while macrovascular complications are cardiovascular events, cerebrovascular diseases, and peripheral vascular diseases (Ministry of Health, 2004). Diabetic microvascular complicationmorbidity was found to be the primarypredisposing factor of end-stage

renal impairment, non-traumatic diabetic foot amputation, and cataractamong adults with diabetes(Sheetz & King, 2002).

In Malaysia, a vast survey on diabetes population showed that 58% ofpatients with diabetes were withneuropathy, 57% with retinopathy, and 52% hadmicroalbuminuria. It was found that 43-52% of diabetic patients were obese and overweight. The majority of them were Malay and Indian females.Moreover, 63-76% had hyperlipidemia(Ministry of Health, 2004). About half of patients with diabetes type 2 are undiagnosed due to silent signs and symptoms (ADA, 2002). As a conclusion, it can be said that Malaysian people are at risk of diabetes complications due to the delayed diagnosis, uncontrolled glycemia and obesity.

1.5 Prevention

Minimizingthe probability of long-term complications of diabetes iscategorized as primary, secondary, and tertiary interventions. The primary type means preventing the complicationsbefore the onset of diabetes, whereas secondary intervention comes afterthe occurrence of diabetes but before the developing diabetic complications. For instance,anti-diabetic treatment is prescribed to reachglycemic controlthat leads to delay the likelihood of microvascular complications, consequently, decreases the rateof deterioration(UKPDS, 1998a). After the occurrence of complications, tertiary intervention might play a role but before the advanced end-stageconsequence (Home, 1996). Using of angiotensin converting enzymeinhibitors (ACEI) was found to decrease the end stage renal disease (ESRD) risk.Similarly, it has been found that laser photocoagulation decreases the risk of severe loss of vision, while preventive foot care decreases the chance of lower limbs amputation in patients with diabetes.

Factors such as routine screening, demographic factors, genetic factor, BMI, physical activity, history of gestational diabetes are identifiers of peopleat high risk of diabetes. Laboratory tests such as insulinsensitivity test and glucose tolerance tests are vital for early diagnosis of diabetes. They are known to influence the risk of progressionto diabetes mellitus to its complications through early diagnosis ("Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group," 1979).

Adivergentlink between diabetes and moderate exercise was revealed by epidemiologic studies (Eriksson & Lindgarde, 1990; Manson *et al.*, 1991). Trials to decrease or prevent obesity such as, low fatty food intake, complex carbohydrates intake and continuous exercise was associated with reduced insulin resistance and incidence of diabetes (Pan *et al.*, 1997).

It was found that 10% of impaired glucose tolerance might develop to diabetes per year, and certain ethnic groups are probably had high risk of diabetes mellitus than others. Moreover, this threatmight be seen amongfemales with positive history of gestational diabetes (Edelstein *et al.*, 1997).

Serious complications such as cardiovascular diseases (CVD) are the leading cause of death amongpatients with diabetes (UKPDS, 1998b). It has been reported that decreasing the risk of 12% of any complications is correlated with reduction of 10 mmHg in mean systolic blood pressure. In details, 15% reduction was for diabetes-related death, 13% of microvascular complications, and 11% of myocardial infarction (MI) amongpatients with diabetes(UKPDS, 1998a). One studyhas shown that the good control for blood pressure is positively associated with the improvement of CVD outcomes in patients with diabetes, especially stroke(Chobanian *et al.*, 2003; UKPDS,

1998b). Moreover, it decreases the rate of CVD by 33-50%(UKPDS, 1998b). This might also delay orprevent diabetic nephropathy (ADA, 2005).

Microvascular complications such as nephropathy was found in about 20-30% of patients with type 2 diabetes (Dobesh, 2006). Untreated neuropathy eventually leads to ESRD(Sowers, 2003). A clinical trial found that 2% of diabetes type 2patients developed microalbuminuria annually. Moreover, 2.8% of them progressed frommicroalbuminuria to macroalbuminuria, and 2.3%progressed from macroalbuminuria to high serum creatinine level (≥ 175μmol/l) or hemodialysis yearly (*U S Renal Data System, USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, 2012). Furthermore, diabetes type 2 nephropathy that cannot be corrected by hemodialysis or kidney transplant increases the risk of cardiovascular morbidity and mortality(Gerstein *et al.*, 2001).Clinical trials revealed that angiotensin-converting enzyme inhibitors (ACEI) andangiotensin II-receptor blockers (ARBs)that suppress renin-angiotensin system RAS are useful in preventingdiabetic nephropathy in addition to their ability to lower bloodpressure (Lewis *et al.*, 2001; "Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data," 2001).

Diabetic retinopathy is a vascular complication with high specificity of both type 1 and 2 diabetes.Retinopathy prevalence is associated with long exposure to diabetes (ADA, 2008). It is the most commonleading cause ofcataracts, glaucoma, and blindness among elderly patients with diabetes.Large prospective randomized studies approved that intensive diabetes management toachieve controlled glycemia wasshowed to prevent and/or delay the onset of diabetic retinopathy(ADA, 2008).

One of the most common diabetes complications is diabetic neuropathy. It can be defined as peripheral nerve impairment signs and symptoms where other causes of peripheral nerve impairment are excluded. This complication accounts forhospitalization more oftencompared with other complications of diabetes as it isthe most commonleading condition of non-traumaticamputation(Bansal, Kalita, & Misra, 2006). Silent myocardial infarction might be caused by diabetic autonomic neuropathy. In addition, diabetes neuropathy was found toshorten the survival rate, causing death in 25%–50% patients with diabetes who had autonomic diabetic neuropathy for 5–10 years. It has been demonstrated that theincidence of neuropathy increased from 7.5% onadmission to 50% at 25 years follow up(cited in (Bansal *et al.*, 2006).

Some studies, (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Gregg *et al.*, 2000; Wilson *et al.*, 2005; Wilson *et al.*, 2002)have tested the relation of diabetes and changes in cognitive function usingdifferent cognitive ways of assessment. However, many facts are still unknown about diabetes and change in different cognitive domains. Numbers of studies were conducted to clarify this relationship. This clarification might also be useful to study the associationof diabetes mellitus with Alzheimer's disease (AD) as cognitive dysfunction is the predisposing factor for dementia or AD(Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004).

1.6 Glycosylated hemoglobin (HbA1c), glycemia control and compliance

Glycosylated hemoglobin is an accurate test to evaluate glycemic control and compliance over a3-month period of time. This test is based on measuring the percentage of red blood cell (RBC) that has beenirreversibly glycosylated at the β-chain N-terminal. This test is considered as an assessment for glycemic control for the last 2-3 months as RBC life span is around 120 days (Parchman, Pugh, Romero, & Bowers, 2007). The normalvalue is between 4-6% of the total hemoglobin (Goldstein *et al.*, 2004). Thetargetfor diabetes is < 6.5% (Ministry of Health, 2004).During conditions such as anemia, acute or chronic blood loss and uremia HbA1c value is affected since these conditions are associated with RBC life span changes. Consequently, these changes lead to flawed assessment for glycemic control(Ceriello *et al.*, 1991).

In fact HbA1c test needsspecial preparations to be conducted such as fasting. This test should not be considered asa replacement for FPG concentration that is importantfor detecting the acute change in blood glucose concentration(ADA, 2010).

1.7 Cognitive function

It refers to mental processing thatcomprised attention, memory, solving problems, producing and understanding language, and making decisions. The term "cognitive dysfunction" is very nonspecific (Ott *et al.*, 1999).Ittypically refers to mild cognitive impairment (MCI), delirium, and dementia. MCI refers to deficiency in memory, language, executive function, or other cognitive domains and is often considered as the early stage of dementia and Alzheimer's disease(AD) (between normal forgetfulness and dementia)(Morris Jc & et al., 2001; Nasreddine *et al.*, 2005).One of the causes that lead to the underestimation of its prevalence is that the dysfunction is often mild.In fact, cognition is a very multifacetedissue and, formerly, it was denied

to exist (Kodl & Seaquist, 2008). Cognitive dysfunction now is studied independently as a medical condition or syndrome instead of being under fatigue and depression. Cognitive assessment methods werealso improved significantly with proper studies on cognitive impairment(Kodl & Seaquist, 2008). While neither MCI nor dementia is an immediate threat of morbidity or mortality, dementia is a proven independent predictor of functional decline, and institutionalization(Cukierman, Gerstein, & Williamson, 2005). Both types of diabetes have been linked with the impaired performance on different cognitive domains(Kodl & Seaquist, 2008; Munshi *et al.*, 2006). The specific pathophysiological changes of cognitive dysfunction in diabetes are not entirelyclear yet.Probably, cognitive changes are affected by hyperglycemia, hypoglycemia, vascular disease, and insulin resistance (Kodl & Seaquist, 2008).Many methodologies to clarify the impact of diabetes on the brain have been developed and conducted. Yet, the most fitting methods to detect, manage, and prevent cognitive impairment among patients with diabetes have not been defined yet (Kodl & Seaquist, 2008).

1.7.1 Cognition and diabetes type 1: Possible underlying mechanism of cognitive dysfunction

Multiple factors appear to be affecting the pathological changes that might lead to cerebral dysfunction among patients with diabetes type 1. Those factors' contribution might be different from one patient to another depending on certain factors like co-morbidity conditions, age, gender, and glycemic control of each patient.

1.7.1(a)Cerebral dysfunction in diabetes type1

Type 1 diabetes patients are prescribed insulin exogenously. Unluckily, by all means and dosage forms, exogenous insulinis unable toachieve the optimum insulin levelcompletely as in normally functioning pancreas. Consequently, those patients have the possibility to show blood glucose levels fluctuations during the day, fromhyperglycemia to hypoglycemia and vice versa. These fluctuations are dependent on the amount and food quality, timing, dose of insulin administered, and the exercise. These fluctuations of glucose level may affect cognitive performance since normal brain function depends on adequate content of glucose level in blood circulation, (ADA, 2002).Nowadays, there are significant evidences that acute disturbance in blood glucose level affects the functioning of the central nervous system (CNS).This may present itself as structural and neurophysiological changes(Weinger & Jacobson, 1998),however, the clinical signs and symptomsare still heterogeneous. This study will take a look into the prevalence of cognitive impairment and the possible risk factors that have been concerned in cognitive function changing in diabetes that may trigger cognitive dysfunction.

1.7.1(b)Cerebral neuroradiological changes

Studies concerning brain neuroradiological changes were few. These studies conducted in patients with type 1 diabetes involved a case-control methodology(Lunetta *et al.*, 1994), whereas others compared patients to standard values(Araki *et al.*, 1994). In a case-control study design, central and peripheral changes have been noticed(Lunetta *et al.*, 1994). Since the majority of MRI reports of patients type 1 diabetic were within normal spectrum,some researchers did not read this as a specific characteristic of diabetes itself (Chabriat *et al.*, 1994). The MRI brain in patients with diabetes has been suggested to resemble that of ageing process,

howeverit was shown to appearin younger patients than in controls(Araki *et al.*, 1994).In general, focal lesions were found in the subcortical white-matter (Ferguson *et al.*, 2003). Hyper-intensity periventricular white-matter lesions, in particular, small punctuate lesions, were present in one third of the scanned patients. These changes was found to be associated with positive retinopathy history (Ferguson *et al.*, 2003).

1.7.1(c)Case-control cognitive performance

Wide spectrum cognitive tests revealed that type 1 diabetes patients have shownmoderate cognitiveimpairment compared to controls. By using diversity of neuropsychological tests, many studies showed that patients with type 1 diabetes performedcompared to controls. Almost all these studies showed negativeimpact on attention, psychomotor speed, general intellectual functioning and delayed memory(Stewart, Prince, & Mann, 2003). A detailed analysis showed that elderly patients with diabetes type 1 performed to some extent poorer on the majority of cognitive domains. These poor performances did not come withnoticeableradiological changes on MRI brain. Yet, it was important to report the level of performance of these elderlywith diabetes type 1 compared with control individualswhich wasparallel to the results in younger adults with type 1 diabetes (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005).Severe cognitive dysfunction have been reported in case studies(Gold *et al.*, 1994).

1.7.1(d)Repeated episodes of severe hypoglycemia

A number of cross-sectionalresearches reported a link between frequently occurred severe hypoglycemia episodes and MCI(Gold *et al.*, 1994; Sachon *et al.*, 1992). However, other studies did not confirm this fact (DCCT, 1996; Kramer *et al.*, 1998; Reichard, Pihl, Rosenqvist, & Sule, 1996). The Diabetes Control and Complications

Trial (DCCT, 1996) was a longitudinal study with 6.5 years average of follow-up that studied the effect of intensive diabetes mellitus treatment on microvascular complications among large sample size patients with type 1 diabetes. It was found that the onset as well as extent diabetic complications such as neuropathy and retinopathy are delayed by intensive diabetes therapyin comparisonwith conventional treatment. The risk of episodes of severe hypoglycemia is increased by threefold using intensive anti-diabetic treatment; however, it was not associated with neuropsychological deficit(Reichard, Britz, & Rosenqvist, 1991). Results suggested that the harmfulimpactof recurring severe hypoglycemia episodes on cognitive performance is limited.

1.7.1(e)Diabetes duration and the presence of other complications

In most cases,diabetes duration and the extent of metabolic control determine the development of diabetic complications (retinopathy, neuropathy and nephropathy). The association of these complications and cognitive performance was reported by several studies (Ferguson *et al.*, 2003; Ryan *et al.*, 2006). The aforementioned associationexplains that the brain is liable to the same changes that cause these other diabetic complications. In fact, thoroughdata on the relation between diabetes duration metabolic control and cognitive function are deficient. The suggestion of thesusceptibility of elderly patients to the diabetes effect on the brainby time makes the missing data on elderly crucial issue.

1.7.1(f)Depression and anxiety morbidity in diabetes

Depression and anxiety disorders was shown to have negative impact on cognitive function especially among diabetes patients that might be attributed to the functionally defective neurotransmitters in the brain (Anderson, Freedland, Clouse,

&Lustman, 2001). A 42-study meta-analysis showed that diabetes doubles the odd ratio of cognitive dysfunction. Moreover, the difference between type 1 and 2 odd ratios was not recognized (Anderson *et al.*, 2001).

1.7.1(g)Hyperglycemia

Like in peripheral tissues, hyperglycemia leads to increase the glucose level in the brain. The extra glucose will convert to fructose and sorbitol (Bhardwaj, Sandhu, Sharma, & Kaur, 1999). Animal studies revealed that the high concentration of sorbitol and fructose in the Central Nervous System (CNS) has been associated to phosphoinositide and diacylglycerol metabolism changes (Bhardwaj *et al.*, 1999). In addition to Ca^{2+} homeostasis changes (Biessels, ter Laak, Hamers, & Gispen, 2002), this will influence the protein kinases activity in the CNS. Animal models demonstrated that protein kinases A and C activities were revealed to be elevated(Bhardwaj *et al.*, 1999). Moreover, otheranimal studies showed that the formation of advanced glycation end products is caused by elevated glucose levels(Brownlee, 1992). These end products was found in the CNS of diabetic rodents (Ryle, Leow, & Donaghy, 1997). Also, glucose toxicity was found to result from thediscrepancybetweenreactive oxygen free radicals production and scavengers(Van Dam & Bravenboer, 1997). Animal studies on diabetic rats demonstrated high concentrations of lipid peroxidation by-products in addition to vertebral oxidative damage(Kumar & Menon, 1993; Mooradian, 1995). Moreover, it was approved that the activities of superoxide dismutase and catalase enzymesthat wereinvolved in the antioxidant protectionpathway of the brain,were decreased (Mooradian, 1995).

1.7.1(h)Cerebrovascular changes

Structural and functional changes in brain tissue that result from diabetes increase the risk of stroke(Beckman, Creager, & Libby, 2002), and atherosclerotic diseases (Mankovsky, Metzger, Molitch, & Biller, 1996). Both conditions might affect cognitive functions. Functional changes in the vasculatureof the brain that have been linked with diabetes type 1 include decreased blood flow in brain, in particular regions in the brain (Keymeulen *et al.*, 1995).Cerebral atrophy is another issue that is generally modest among patients with type 1 which might affect cognitive functions. This issue needs further investigations (Sabri *et al.*, 2000).

1.7.1(i)The role of severe prolonged hypoglycemic episodes

Brain damage may be provoked by prolonged hypoglycemia. This can be explained by the uncontrolled release of glutamate and aspartate (excitatory amino-acids), activate calcium influx which will lead to proteolytic enzymes activation. This process will causeneurons damage (Perros & Frier, 1997). In addition, experimental design found that the duration of hypoglycemia episodes also affects brain damage severity (Chabriat *et al.*, 1994). During the glucose shortage period in the brain, alternatives such as amino-acids and ketones will act as fuel resource. These alternatives will lead to brain damage(Chabriat *et al.*, 1994).

1.7.1(j)The insulin role in the brain

The hippocampus is a major brain structure that play an important role in memory function, especially the long-term consolidation of information (forming, organizing and storing).A considerable number of insulin receptors are present in hippocampus (Park, 2001). It has been found that insulin can modulate memory function by several mechanisms. Insulin is found to be helpful glucose utilization in certain areas in

brain,such as the hippocampus. In addition, it has been suggested that glucose play an important role to promote memory tasks(Park, 2001). Suggestion was made also about the indirect role of insulinto promote the neurotransmitters activity such as acetylcholine by stimulating the uptake of glucose by neurons (Park, 2001). These neurotransmitters were found to have major role in memory consolidating (Park, 2001).

Under abnormal conditionssuch as diabetes type 1,endogenous insulin secretion by the β-cells is almost absent. In such condition, the use of exogenous insulin subcutaneously asa replacement is the treatment of choice. Consequently, the level of insulin in the blood is elevated(Nijs, Radder, Poorthuis, & Krans, 1990). Insulin needs to pass the blood brain barrier to reach and bind to its receptors in the brain to exert its effect. This process is affected by diabetes mechanism as a disease. Animal study showed that insulin transport through the blood brain barrier is increased during hyperglycemic, hypoinsolinimic diabetic type 1 rodent (Banks, Jaspan, & Kastin, 1997).In addition, it has been reported that insulin-receptors binding in the brain of these rodentsdoes not differ from controls (Marks & Eastman, 1989). In addition,it was shown to be lower in high insulin level, high glucose level rodents brains(Figlewicz *et al.*, 1985).

In fact, types of diabetes might be differentin insulin signaling.It is well understood that diabetes type 2is highly associated with insulin resistance, whereas diabetes type 1 is associated with this insulin resistance to a lesser extentthan type 1(DeFronzo, Hendler, & Simonson, 1982).The literature gave an explanation to a part of the distinctive cognitive profiles of these two types. For instance, in diabetes type 1, long term storage of information and recall of information seems to be comparatively intact unlikediabetes type 2 patients. Long term storage of information and attainment of

information are mainly processed in the hippocampal region in the brain that has high number of insulin receptors that make it extra susceptible to any defect in insulin action (Squire & Alvarez, 1995).

1.7.2 Cognition and diabetes type 2

1.7.2(a)Demographic factors

Recently, it was obvious that diabetes type 2 affectsthe CNS in many pathways(Gispen & Biessels, 2000). The literature dealt with the cognitive functioning and diabetes type 2relationship, in particular, with certain cognitive domains such as verbal memory or complex information processing(Awad, Gagnon, & Messier, 2004). These studies differ in terms of demographic criteria of participants, like age, gender distribution, diabetic parameters (diabetic complications, diabetes treatment, and diabetic duration) (Awad *et al.*, 2004; Stewart & Liolitsa, 1999). Different methodologies were adopted in those studies. In addition, differentcognitive domains were the point of interest. Regardless of these differences, the most common result is that mild to moderate cognitive dysfunction (information processing speed, episodic memory and, to a less extent, mental flexibility) is associated with diabetes type 2 (Awad *et al.*, 2004; Stewart & Liolitsa, 1999).

1.7.2(b)Glycemic control and its related problems

Studies tested relations between cognitive functioning and different disease variables demonstrated that cognitive impairment was associated with worse glycemic control (Strachan, Deary, Ewing, & Frier, 1997). Cognitive dysfunction is also thought to be enhanced by other risk factors (cardiovascular, cerebrovascular disease, and depression). Furthermore, age has not been used as a dependent variable in nearly most of studies.Mostly, the literature dealt with patients who were among older age

group(Ryan & Geckle, 2000). As patients with type 2 getting older, other conditions such as hypertension, macro- and microvascular complications, atherosclerotic changes will be developed(Manschot *et al.*, 2006; Ryan & Geckle, 2000). Those conditions may produce further cognitive dysfunction.

Some epidemiological studies revealed a relation between diabetes and dementia (Leibson *et al.*, 1997; Ott *et al.*, 1999). The mediators that accelerate cognitive impairment in patients with diabetes type 2 are not clear yet. Studies in this field concerned both, diabetic complications (for example, hypertension and depression) and glycemic control (Allen, Frier, & Strachan, 2004; Stewart & Liolitsa, 1999). Few studiesconsidered hypertension as a vital risk factor for cognitive impairment(Alexopoulos *et al.*, 1997; Hassing *et al.*, 2004; Stewart & Liolitsa, 1999). On the other hand, other studies did not support these findings (Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004; Luchsinger *et al.*, 2005).

1.7.2(c) Cerebral radiological changes

Abnormal MRI cerebral was highly considered in only few studies in patients with diabetes type 2. Case-control studies addressed that subcortical and cortical atrophy and symptomatic and silentbrain infarcts were in found patients with diabetes type 2 compared to controls (Araki *et al.*, 1994; Manschot *et al.*, 2006; Vermeer *et al.*, 2003). It was shown that abnormal MRI changes were associated with cognitive dysfunction, mostly, atrophy, lesions, and infarcts in the white-matter.

1.7.2(d) Neuropsychological changes

Type 2 is also associated with depressive symptoms (Anderson *et al.*, 2001; Lockwood, Alexopoulos, & van Gorp, 2002) that might be also associated with cognitive dysfunction (Lockwood, Alexopoulos, & van Gorp, 2002; (Elderkin-

Thompson *et al.*, 2003). Also, depressive symptoms were addressed to be related to white-matter abnormalities (Jorm *et al.*, 2005). Moreover, it is associated with the extent of diabetic complications which has been addressed as vascular depression (Alexopoulos *et al.*, 1997). Among elderly subjects, the co-occurrence of the three conditions (depressive symptoms, cognitive dysfunction, and vascular abnormalities) was addressed as vascular dementia or pseudo-dementia. In another word, areversible cognitive dysfunction is associated with geriatric vascular depression (Baldwin, Gallagley, Gourlay, Jackson, & Burns, 2006).

1.7.2(e) Type 2 diabetes treatment

A study revealed that Roziglitazone might improve cognition in patient with Alzheimer disease (Brodbeck *et al.*, 2008), and metformin monotherapy might increase the formation of beta-amyloid protein, a predisposing factor of cognitive dysfunction and Alzheimer disease. It has been found that metformin combination therapy with TZDs, or with insulin is considered as a cognitive function protector (Chen *et al.*, 2009).

In conclusion, the need for further studies to reveal the predisposing factor(s) for cognitive impairment among patients with diabetes is mandatory. It is important to go further andinvestigate the diversity between diabetes type 1 and type 2 regarding their association with cognition changes. It was shown that the two types of diabetes are characterized by distinctivemodels of cognitive dysfunction. Further illumination is needed to see whether these distinctive models are due to the role of insulin in the brain in each type, or due to the fact that studies on type 2 diabetes and oral anti-diabetic drugswere mostly performed with elderly patients in comparison with those studies on diabetes type 1.

1.8 Problem Statement

Diabetes mellitus have been linked with shortages in certain number of mental processing domains of cognitive performance with unclear mechanism. This disease thought to be one of the predisposing factors of cognitive impairment. At the same time, diabetes is a self-management metabolic disease that needs intact cognition. The importance of this appears in dealing with diabetes treatment and its high complexity. For example patient with diabetes need intact cognition to deal with conditions such asmonitoring of blood glucose level, diet regimen, and compliance to medications and their complex timetable.Considering the importance of intact cognition in these conditions, patientswho show cognitive problemshave significant possibility to face difficulties to manage their conditions. For example, patients might forget about their medication timing or dosing. They may also have difficulty in treating acute conditions associated with diabetes treatment such as hypoglycemia. In addition, those patients considered as incapable to reportor even realize both conditions, the cognitive problems and/or thecomplexityofmanaging diabetes on their own. For that reason, medical care givers might be unaware of cognitive impairment (Munshi *et al.*, 2006), and that calls for need for cognitive assessment.

This studytend to combine cognitive data, data on psychological well-being,and diabetes clinical information using a reasonably sufficient number of patients with type 1 and type 2 diabetes. In addition, the same data were collected from a number of control subjects. The controls were with certain criteria, age, and educational level-matched control participants.Small sample MRI screening data analysis was also adopted. This combination, in the researcher's opinion, adds new insights to the present literature. This study will raise the following questions: