International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518

The Relationship between Type 2 Diabetes Mellitus and Dementia in Elderly.

Rawan. M. Almatrafi

Abstract:-

Background: Diabetes Mellitus is one of the most common chronic disease specifically in aging population. Diabetes results from increase the level of blood glucose. There are many complications that associated with diabetes like cognitive decline.

Objectives: The review aim to provide overview to T2DM and its pathogenesis. Also, to clarify the pathogenesis of dementia and the association between type 2 diabetes and dementia in elderly.

Review of literature : High glucose level will cause accumulation of advanced glycation end products. These products have likely toxic effects on neurons and will cause some changes in the structure of hippocampus. Accumulation of AGEs can lead to create oxidative damage, which cause mitochondrial dysfunction. High glucose levels can lead to increased risk of dementia in diabetic patients.

Conclusion: Aging is associated with insulin resistance and mitochondrial dysfunction which can lead to cause type 2 diabetes mellitus. Subsequently, patients with type 2 diabetes mellitus are at higher risk for development of dementia compared with those without diabetes.

Thus, T2DM is strongly related to dementia and cognitive impairment that result from accumulation of Aβ plaques and Tau tangles in AD. The second way, T2DM could induce vascular dementia through alteration in cerebral blood vessels. However, the exact mechanism that link T2DM with AD need more illustration.

Key words: "Aging ", "Alzheimer's disease ", " cognitive dysfunction", " dementia "," insulin resistance " ,"Type 2 diabetes mellitus, and "vascular dementia ".

Abbreviations: (T2DM) Type 2 diabetes mellitus, (AD) Alzheimer's disease (VD) vascular dementia.

INTRODUCTION : -

Diabetes Mellitus is a major metabolic disorder that can have devastating effects on multiple organs in the body. [1] The number of people affected by diabetes in Saudi Arabia was 3.4 million cases in 2015. [2]

Diabetes can cause major public health problem and multiple complications such as renal diseases, vision loss, neuropathy, cardiovascular disease and cognitive dysfunction [3]

There are two major types of diabetes type 1 and type 2. A third type, gestational diabetes, occurs temporarily during the pregnancy. [2] Type 2 diabetes mellitus (T2DM) is resulting from insulin resistance which cause reduced in insulin sensitivity and therefore relative insulin insufficiency. There are many in vivo studies that demonstrate a correlation among the mechanism of insulin resistance, and the formation of plaque and damaged neuronal signaling in AD. [4] T2DM accelerates the cognitive decline in elderly and increased risk of many types of dementia, such as Alzheimer's disease (AD) and vascular dementia (VD). [5]

International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518

Dementia is a "general term for loss of memory and other mental abilities severe enough to interfere with daily life". It is one of the most common disease of later life caused by structural changes in the brain. [4] There are about 4.6 million recent cases of dementia that are predicted worldwide annually. [6]

Alzheimer's disease (AD) is the most common type of dementia caused by formation of the neurofibrillary tangles and neuritic plaques. [7]

Vascular dementia (VD) is the second types, it has developed to occur of stroke which is caused by diseases of small vessels and chronic brain ischemia. [8]

In 2012, the World Health Organization jointly with Alzheimer's disease International published that the number of people who live with dementia worldwide is presently estimated at 35.6 million and will double to 65.7 million by 2030. In 2050, number will increase and may reach 115.4 million. In addition, dementia accounted for 11.2 % of years lived with disability in people aged 60 years or older. [9]

In Saudi Arabia, the most common type is AD (51.9%), while VD (18.2%), mixed dementia (AD and VD) 15.6%, dementia with Parkinson's 7.8% and other types of dementia is 6.5 %. [11]

Objectives: - The purpose of the current review is to provide overview to type 2 diabetes and its pathogenesis. Also, to clarify the pathogenesis of dementia and the association between type 2 diabetes and dementia in elderly.

LITERATURE OF REVIEW:-

i. Overview of Type 2 Diabetes Mellitus: -

Type 2 diabetes mellitus is characterized by increasing in blood glucose levels as a result to interplay of numerous genetic, behavioral and environmental factors that lead to impair of insulin action on target tissues and defective of pancreatic beta cell insulin secretion in response to glucose. [12]

Type 2 diabetes mellitus is one of the most common prevalent of chronic diseases worldwide. Since it represents approximately 90 to 95% of diabetic cases. [13]

A study done by **Naeem Z (2015)** evaluated 16,917 Saudi subjects in the age group of 30–70-years over 5 years. Data were collected from history, body mass index and fasting plasma glucose levels. The data were analyzed to allocate individuals as diabetic, impaired fasting glucose and normal. Four thousand and four subjects (23.7%), out of 16,917 were diagnosed to have DM. Thus, the prevalence of DM obtained from the study was 23.7% in KSA. [14]

- **Main Causes of Type 2 Diabetes Mellitus: -**

A study carried out by **Hu FB et al (2001**), reported that T2DM occurs due to number of lifestyle factors; these are obesity, physical inactivity, smoking, drinking alcohol and sedentary lifestyles. Similarly stated that less active lifestyle and aging, increase the risk of T2DM. [15]

Recent study done by **Olokoba et al (2012)** demonstrated that there is an inheritable genetic relation in T2DM, having relatives increases the risks of developing T2DM substantially. Concordance between monozygotic twins is approximately 100%, and about 25% of those who have a family history of DM. Recently, there is increasing in the rate of occurrence of T2DM and this may due to share of some environmental toxins. [13]

- **Pathogenesis of Type 2 Diabetes: -**

A study done by Taylor (2013) revealed twin cycle hypothesis that demonstrated the pathogenesis of T2DM (Figure 1): -

The first cycle is liver cycle, during high caloric intake for long period, any excess carbohydrate should undergo lipogenesis, which lead to increase fat deposition in the liver. Also, insulin can stimulate de novo lipogenesis, individuals who have an insulin resistance (which determined either by genetic or lifestyle factors) will lead to accumulate fat in the liver. In turn, the increased fatty liver will impair the ability of insulin to suppress the production of hepatic glucose which increase the deposition of fats.

The increase of glucose level in the plasma will lead to stimulate increased basal insulin secretion rates to maintain euglycemia. The hyperinsulinemia will increase the conversion of excess calories to fats which deposit in the liver. Fatty liver cause impaired fasting glucose metabolism and increases export of VLDL triacylglycerol, which lead to increase delivery of fat to all tissues, including the islets. The pancreas cycle starts when excess fatty acids accumulate in the pancreatic islet which lead to impair the secretion of insulin in response to ingested food. Eventually, the fatty acid and glucose inhibitory effects on the islets reach the level that can cause a sudden onset of clinical diabetes. [16]

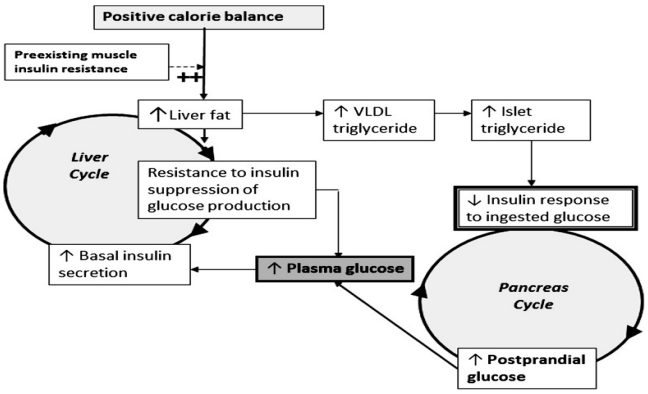

Fig . 1. The twin cycle hypothesis of the etiology of type 2 diabetes. [16]

ii. Type 2 Diabetes and Its Relation to Age: -

A study in 2014 done by **De Ta,** reported that the incidence of T2DM in older adult was more than twice that of middle aged adults and it reached the peak at 60–74 years of age. Normal aging is often correlated with a continuous deterioration in the most of endocrine functions that may lead to sever disturbances in metabolic homeostasis of the body. Actually , aging is considered as the main cause for an

International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518

impairment of glucose tolerance that occur in both humans and experimental animals. This occurs through many factors that mainly lead to beta cell dysfunction and insulin resistance. [17]

1) **Aging and Beta Cells Dysfunction:**

Kushner (2013) reported that pancreatic beta cells have been undergo frequent turnover, studies suggested that cell cycle entry of pancreatic beta cells may be severely limited in elderly. The authors noticed that an aging would lead to increase in lipofuscin content within the human β cells, implying that human β cell turnover happens very intermittently. [18]

In addition, a study done by **De Ta (2014)** demonstrated that the regenerative capacity of the organs decreased with age. Similarly, aging could lead to decline of beta cell proliferation and affection of its secretory capabilities through several attributed factors like: mitochondrial dysfunction, mitochondria play an important role in the physiological stimulus secretion of insulin from beta cells. In these cells, mitochondria are acting as nutrient sensors and signal generators for the secretion of insulin. Thus, any damaging for mitochondria could result in decreased beta cell function and subsequently decreased in insulin secretion. [17]

Also, there are other factors such as telomerase deficiency and reduced the length of telomere which lead to reduce the islet size and impairment in the replication capacity of insulin-producing beta-cells; reduction in the level of glucose transporter 2 (GLUT2) ; formation and accumulation of advanced glycation end products (AGEs) ; reduction in the expression of β2-adrenergic receptors ; reduction in the response to glucagon like peptide-1 (GLP-1) stimulation ; increased autophagy ; reduction in the expression of pancreatic beta cell specific genes and transcription factors such as PDX-1, (Figure 2) . [17]

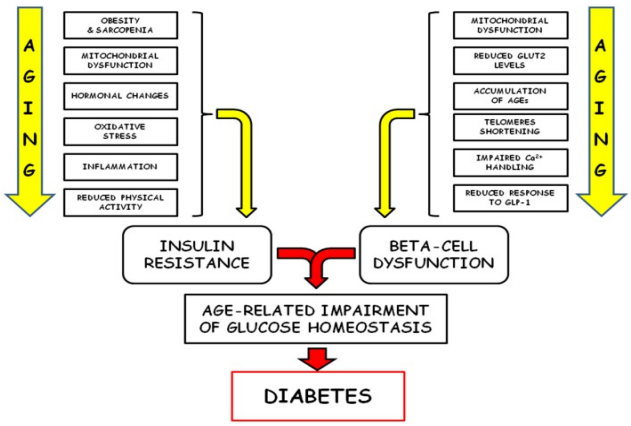

Fig . 2 . Schematic representation of the most important pathophysiological factors which responsible of the age-related failure of glucose homeostasis. [17]

2) **Aging and Insulin Resistance: -**

The term insulin resistance is indicated that requirement of higher than normal circulating levels of insulin is essential to sustain normoglycemia. At the cellular level, insulin action, originated by the binding to its receptor on cell surface, which involves a series of signaling cascades that can be summarized as follows: "receptor autophosphorylation and activation of receptor tyrosine kinase; tyrosine phosphorylation of insulin receptor substrates (IRSs) 1 and 2; activation of phosphatidylinositol 3kinase (PI3K); activation of Akt and its downstream mediator, AS160, which lead to stimulate the translocation of insulin-mediated GLUT4 from intracellular vesicles to the plasma membrane". [17]

A study done by **Evans (2013)** reported that aging is associated with increase nitric oxide (NO) production, especially inducible nitric oxide synthase (iNOS), has also been implicated in insulin resistance. [19]

Also, Insulin resistance occurs due to sharing many factors such as, obesity, mitochondrial dysfunction, oxidative stress, hormonal change and reduced physical activity (Figure. 2). This was in accord with **De Tata (2014)** who stated that aging had a strong association with a decline of insulin action. [17]

iii. Overview of Dementia: -

Chatterjee (2016) demonstrated that dementia is a multifaceted syndrome that lays claim to a growing burden of global disease. The newest estimates suggested that there are 44 million affected individuals worldwide and a about 7.7 million new cases annually. There are many types of dementia but the most common of them are Alzheimer's disease and Vascular dementia. [20]

Dementia is a cognitive impairment. It describes a group of symptoms that happen when brain cells stop working properly due to either accumulation of specific protein or stopping of blood flow to the brain. [21]

- **Main risk factors of dementia:-**

The study done by **Baumgart et al (2015)** believed that there was adequate evidence that support the link among several modifiable risk factors and increased risk for cognitive decline (table 1). However, the strongest risk factors for late onset Alzheimer's disease and other types of dementia were age, family history, and genetic susceptibility genes such as the Apolipoprotein E ε4 allele. [22]

Table 1: -
The main risk factors for dementia. [22]

Modifiable risk factors of dementia
Diabetes
Mid-life obesity
Mid-life hypertension *Hyperlipidemia (elevated cholesterol)*
Traumatic brain injury

1. **Alzheimer's disease (AD):-**

Alzheimer's disease is the most common type of dementia. A study done by **Mckhann, et al (2011)** found that the first symptom of AD was a progressively worsening of the ability to memorize new information. [23]

In addition, there were other symptoms such as; losing memory that affects daily life, challenges in solving

International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518

problems or planning, facing difficulty to complete familiar task at home or work trouble for understanding spatial relationships and visual images, having problems with words in writing or speaking, losing the ability to retrace steps and misplacing for things. [24]
Alzheimer's could be presented with behavioral symptoms for instance; hallucinations, paranoia, delusions, and psychosocial impairment, which could lead to withdrawal from work or social activities. [24]

A recent study done by **Webster et al (2014**) found that increasing in aggressive behaviors were one of the common behavioral symptoms of AD and present themselves in 65% of patients and this occurs due to dysregulation of different neurotransmitter like serotonin, norepinephrine, GABA and dopamine. Also, depressive symptoms were a very common in AD patients. The exact prevalence of this was not known, but was believed to range from as low as 2% to as high as 85%. [25]

- ***The pathogenesis of Alzheimer's disease. :-***

A study conducted by **Alzheimer's Association (2014)** reported that the brain of healthy adult consists approximately of 100 billion neurons, with long, and branching extensions. These extensions help neurons to form connections with other neurons and form synapses, which help transfer the information between neurons. [24]

The number of synapses in our brains are close to 100 trillion synapses. The numerous synapses can allow the signals to travel through the brain's circuits, thoughts, creating the cellular basis of memories, emotions, movements, sensations and skills. Alzheimer's disease effects on the appropriate functioning of neurons and synapses by a progressive loss of neurons in cerebral cortex, especially pyramidal cells, which help to mediate higher cognitive functions. [24]

The previous study showed that Alzheimer's was developed due to accumulation of the protein beta-amyloid outside neurons (called beta-amyloid plaques Aβ). Aβ plaques would cause neurotoxicity and feature of the pathophysiological processes downstream Aβ. Their origin can be axonal or dendritic. Aβ Plaque will lead to desensitization of insulin receptors and decrease synthesis of insulin-degrading enzyme (IDE) which degrades Aβ plaques. [24]

A study done by **Blazquez, et al (2014**) showed that reduction in the amounts of IDE would lead to great deposition of amyloid which cause cells death. [26]

Alzheimer's Association (2014) found that in Alzheimer's disease, the information transfer at synapses began to fail, the number of synapses declines, and neurons eventually die. The brains of people with advanced Alzheimer's showed dramatic decrease in volume and shrinkage due to loss of cell and widespread debris from dead and dying neurons. [24]

In addition, a study carried out by **Bedse, et al (2015)** demonstrated that there was accumulation of tau tangles inside the neurons which could lead to block the transport of nutrients and other essential molecules in the neuron through impaired the insulin signaling which could result in activation of glycogen synthase kinase3β that cause enhancement of phosphorylation of tau protein and formation of neurofibrillary tangles which would cause death of cells. [27]

2. Vascular dementia: -

According to study done by **Lemolo, et al (2009)** demonstrated that vascular dementia meant "disease with a cognitive impairment resulting from cerebrovascular disease and ischemic or hemorrhagic brain injury". It is the second most common type of dementia. [28]

Alzheimer's Society (2014) approved that reducing of blood supply to some region in the brain due to cerebrovascular diseases. The brain cells need a constant blood supply to bring enough oxygen and nutrients to be healthy and to do its function properly. If the vessels in the brain were damaged either they became leaky or blocked then the blood could not reach the brain cells in enough amount and they would finally die. This death of brain cells could lead to problems with thinking, memory or reasoning. Age considered the greatest risk factor for vascular dementia. A person's risk of developing vascular dementia doubles about every five years over the age of 65 years old. However, under the age of 65 vascular dementia was uncommon and affected less than 8,000 people in the UK. Men were at higher risk of vascular dementia than women. [29]

In 2014, the study was done by **Song, et al** revealed that a person who had a previous stroke, diabetes or heart disease, was about twice as likely to develop vascular dementia. There are some studies suggest that a history of depression, cardiovascular disease like hypertension, hypercholesterolemia and being overweight in mid-life may increase the risk of vascular dementia. [30]

iv. T2DM and cognitive dysfunction: -

A cohort of Japanese-Americans in Hawaii study done by **Peila, et al (2002)** showed that type 2 diabetic patients had a 1.8-fold greater risk for developing AD and a 2.3-fold higher risk for vascular VD. [31] This was in accord with a study done by **Arvanitakis, et al (2004)** who demonstrated that T2DM subjects approximately have 65% risk of developing AD. [32]

In contrast, a study done by **Schneider et al (2006)** on 233 older subjects, about 15 % of them are diabetic patients. The study showed that T2DM was associated with increased odds of infarction (OR = 2.47, 95% CI: 1.16, 5.24). However, there was not associated with AD pathology. [33]

In other hand, A meta-analysis studies done by **Cheng, et al (2012)** demonstrated that the relative risk of AD among 506 subjects with T2DM was 1.46 (1.20–1.77) compared with 36,191 subjects without T2DM. For vascular dementia, the relative risk was 2.5 (2.1–3.0), between 3,519 subjects with T2DM and 23,026 subjects without. [34]

The prevalence of DM in Saudi Arabia is very high. In a study carried out by **Ghassan (2016)** evaluated the influence of type 2 diabetes mellitus on cognitive function. The study started from June to July 2012 in the outpatient department of King Abdulaziz University Hospital (KAUH), Jeddah, this study admitted a total of 171 outpatients with diabetes, matched with 68 controls if they were aged 45 years old or more than it. The participants underwent some cognitive assessments such as the Montreal Cognitive Assessment Test (MoCA), and the Rowland Universal Dementia Assessment Scale (RUDAS). Diabetic patients were more acceptable to

International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518

have less performance than controls in term of RUDAS score, and this association perseveres after adjustment for age, gender, education level. [35]

v. Underlying mechanism of cognitive dysfunction in T2DM

Umegaki (2014) found that the exact mechanism underlying T2DM was related to the development of dementia, especially Alzheimer's disease was needed more illustration. However, there were many hypothetical mechanisms have been proposed. [5]

- **Insulin Resistance (IR): -**

The abnormalities of blood glucose and IR may be associated with acetylcholine (Ach) synthesis because insulin help in regulation of Ach transferase expression. Ach is a neurotransmitter which has a critical role in cognitive function, it may cause cognitive impairment in diabetic patients. [5]

- **Neurogenesis: -**

A study conducted by **Lang, et al (2009)** showed that T2DM could decline the neurogenesis that happen in the hippocampus region which plays an important role in memory and learning. [36]

- **Vascular dysfunction: -**

De Bresser, et al (2010) reported that dysfunction of cerebral autoregulation with increasing age along with structural and functional changes in cerebral blood vessels due to diabetes mellitus. These phenomena may cause functional deficits in neurons and which lead to increase in neuronal degeneration and the susceptibility to hypoxia and ischemia. Also, impaired neurovascular units would cause BBB leakage. Recently, the hypothesis of vascular dysfunction may impair the drainage pathways of Aβ from the brain parenchyma and thus increase accumulation of Aβ plaques have been drawing interest. Vascular dysfunction could be associated with the progression of amyloid pathology. [37]

- **Blood–brain barrier (BBB): -**

A study done by **Umegaki (2014)** showed that diabetes was associated with BBB dysfunction which may cause cognitive impairment. The previous observations for biopsy that took from brain tissue of AD subjects showed BBB breakdown in several respects. These include thickening of the basement membranes, thinning of the endothelium, mitochondrial dysfunction, and increase the accumulation of focal Aβ peptides. [5]

- **Hyperglycemia: -**

A recent longitudinal study over 6 years which done by **Crane, et al (2013)** also reported higher level of blood glucose could increase risk of dementia in both diabetes and non-diabetes subjects. [38]

A study done by **Umegaki, (2014)** found that high blood glucose level would cause forming of advanced glycation end products (AGEs). These products had potentially toxic effects on neurons and would cause multiple changes in the structure of hippocampus. AGEs with free radicals could lead to create oxidative damage, which would cause mitochondrial dysfunction. [5]

- **Inflammatory mechanism: -**

A study conducted by **Badawi, et al (2010)** showed that inflammations had an important role in insulin resistance and T2DM. The innate immunity that stimulated in response to multiple genetic and environmental factors could lead to activation of macrophages and release inflammatory cytokines which lead to downstream for insulin signal and activation of glia which cause damages the neurons. [39]

CONCLUSION:-

The aim of this literature review was to provide an overview to T2DM mellitus and its pathogenesis, to clarify the pathogenesis of dementia and to determine the relationship between type 2 diabetes mellitus and dementia (AD and VD) in elderly.

Aging is associated with insulin resistance, mitochondrial dysfunction and beta cell dysfunction which can lead to cause T2DM. Subsequently, patients with type 2 diabetes are at higher risk for development of dementia.
Thus, T2DM is strongly related to dementia and cognitive impairment that result from accumulation of Aβ plaques and Tau tangles in AD. Therefore, T2DM can accelerate the pathologies of AD, which can lead to neurodegeneration and brain atrophy. The second way, T2DM could induce vascular dementia through alteration in cerebral blood vessels that result either by breaking down of BBB or progression of amyloid pathology. However, the exact mechanism that link T2DM with AD need more illustration.

ACKNOWLEDGEMENT: -

I would like to thank my supervisor Dr. Ghada Wassif for support me during the writing process. Also, I would like to express my appreciation to each of Taibah University for their providing easy ways to access to resources through the e-library.

REFERENCES:-

1. The Global Diabetes Scorecard [Internet]. The Global Diabetes Scorecard. 2017 [cited 9 April 2017]. Available from: http://www.idf.org/global-diabetes-scorecard/

2. **Omiepirisa Yvonne Buowari**. Diabetes Mellitus in Developing Countries and Case Series [Internet]. 1st ed. nigeria: Oluwafemi O. Oguntibeju; 2013 [cited 6 April 2017]. Available from: https://cdn.intechopen.com/pdfs-wm/42090.pdf

3. **Chentli F, Azzoug S, Mahgoun S**. Diabetes mellitus in elderly. Indian J Endocrinol Metab. 2015; 19(6):744-752. Available from: http://www.ijem.in/article.asp?issn=2230-

4. **El Khoury NB, Gratuze M, Papon M-A, Bretteville A, Planel E**. Insulin dysfunction and Tau pathology. Front Cell Neurosci. 2014;8:22.Available from : http://www.frontiersin.org/Journal/Abstract.aspx?s=156& name=cellular%20neuroscience&ART_DOI=10.3389/fncel.2014.00022

International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518

5. **Umegaki H**. Type 2 diabetes as a risk factor for cognitive impairment: current insights. Clin Interv Aging. 2014;9:1011-1019.Available from :https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085321/

6. **Ferri CP, Prince M, Brayne C, et al**. Global prevalence of dementia: a Delphi consensus study. Lancet.2005;366(9503):2112-2117.available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2850264/

7. **Fratiglioni L, Winblad B, von Strauss E.** Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project. Physiol Behav 2007; 92(1-2): 98-104. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17588621

8. **Weintraub S, Wicklund AH, Salmon DP**. The Neuropsychological Profile of Alzheimer Disease. Cold Spring Harbor Perspectives in Medicine.2012;2(4):a006171 Available from: https://www.ncbi.nlm.nih.gov/pubmed/22474609

9. **Kalaria RN.** Vascular Basis for Brain Degeneration: Faltering Controls and Risk Factors for Dementia. Nutrition reviews. 2010; 68(Suppl 2):S74-S87. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058404/

10. **World Health Organization and Alzheimer's disease International.** Dementia. A public health priority. Available at: http://www.who.int/mental_health/publications/dementia_report_2012/en/ Accessed 2 April 2017

11. The Arab Journal of Psychiatry (2013) Vol. 24 No. 1 Page (77 - 84)

12. Types of Diabetes [Internet]. Canadian Diabetes Association. 2017 [cited 9 April 2017]. Available from: http://www.diabetes.ca/about-diabetes/types-of-diabetes

13. **Olokoba AB, Obateru OA, Olokoba LB**. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Med J. 2012; 27(4):269-273. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3464757/

14. **Naeem Z.** Burden of Diabetes Mellitus in Saudi Arabia. Int J Health Sci. 2015; 9(3): V-VI. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4633187/

15. **Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al.** Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001. Sep; 345(11):790-797. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11556298

16. **Taylor R.** Type 2 Diabetes: Etiology and reversibility. Diabetes Care. 2013; 36(4):1047-1055. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609491/

17. **De Tata V.** Age-Related Impairment of Pancreatic Beta-Cell Function: Pathophysiological and Cellular Mechanisms. Front Endocrinol (Lausanne). 2014; 138(5):1-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4153315/

18. **Kushner JA.** The role of aging upon β cell turnover. J Clin Invest.2013; 123(3):990-995. Available from : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3582123/

19. **Evans JL, Goldfine ID.** Aging and Insulin Resistance: Just Say iNOS. Diabetes. 2013;62(2):346-348.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3554381/

20. **Chatterjee S, Peters S, Woodward M, Arango S, Batty G, Beckett N et al .** Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia. Diabetes Care. 2015; 39:300-307. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26681727

21. **Alzheimer's Association**. BASICS OF ALZHEIMER'S DISEASE [Internet]. 1st ed. Alzheimer's Association; 2016 [cited 9 April 2017]. Available from: https://www.alz.org/national/documents/brochure_basicsofalz_low.pdf

22. **Baumgart M, Snyder H, Carrillo M, Fazio S, Kim H, Johns H**. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's & Dementia. 2015; 11(6):718-726. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26045020

23. **McKhann GM, Knopman DS, Chertkow H, et al.** The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3): 263-269. Available from: https://www.alz.org/documents_custom/Diagnostic_Recommendations_Alz_proof.pdf.

24. **Alzheimer's Association.** Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2014; 10(2):e47-e92. Available from: http://www.sciencedirect.com/science/article/pii/S1552526014000624

25. **Webster S, Bachstetter A, Nelson P, Schmitt F, Van Eldik L**. Using mice to model Alzheimer's dementia: an overview of the clinical disease and the preclinical

International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518

behavioral changes in 10 mouse models. Front Genet. 2014; 5. Available from: http://journal.frontiersin.org/article/10.3389/fgene.2014.00088/full

26. **Blázquez E, Velázquez E, Hurtado-Carneiro V, Ruiz-Albusac JM**. Insulin in the Brain: Its Pathophysiological Implications for States Related with Central Insulin Resistance, Type 2 Diabetes and Alzheimer's disease. Front Endocrinol (Lausanne). 2014; 5:161. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4191295/

27. **Bedse G, Di Domenico F, Serviddio G, Cassano T.** Aberrant insulin signaling in Alzheimer's disease: current knowledge. Front Neurosci. 2015; 9:204. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4468388/

28. **Iemolo F, Duro G, Rizzo C, Castiglia L, Hachinski V, Caruso C**. Pathophysiology of vascular dementia. Immun Ageing : I & A. 2009; 6:13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2784430/

29. **Alzheimer's Society.** What is vascular dementia? 1st ed. England: Alzheimer's Society; 2017. Available from: https://www.google.ae/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwiT3bfvurXTAhVOY1AKHfhpBlAQFggiMAA&url=https%3A%2F%2Fwww.alzheimers.org.uk%2Fdownload%2Fdownloads%2Fid%2F2427%2Ffactsheet_what_is_vascular_dementia.pdf&usg=AFQjCNEcWBC_g0n66LFFfH2zGHpcEXM2pQ

30. **Song J, Lee WT, Park KA, Lee JE.** Association between Risk Factors for Vascular Dementia and Adiponectin. Biomed Res Int. 2014; 2014:261672. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4016875/

31. **Peila R, Rodriguez BL, Launer LJ, Honolulu-Asia.** Aging Study Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies:

32. **Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA.** Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol. 2004; 61(5):661–666. Available from; https://www.ncbi.nlm.nih.gov/pubmed/15148141

33. **Arvanitakis Z, Schneider J, Wilson R, Li Y, Arnold S, Wang Z et al**. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Front Aging Neurosci. 2006; 67(11):1960-1965. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17159101

34. **Cheng G, Huang C, Deng H, Wang H.** Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J. 2012; 42(5):484–491. Available from : https://www.ncbi.nlm.nih.gov/pubmed/22372522

35. **Alaama T, Basheikh M, Khiyami A , Mutwalli M, Batawi S, Watfa G.** Diabetes status is associated with poor cognitive performance in Saudi population at high metabolic risk. JARCP.2016; 5(4):170-174. Available from: http://www.jarcp.com/3213-diabetes-status-is-associated-with-poor-cognitive-performace-in-saudi-population-at-high-metabolic-risk.html

36. **Lang BT, Yan Y, Dempsey RJ, Vemuganti R**. Impaired neurogenesis in adult type-2 diabetic rats. Brain Res. 2009; 1258:25–33. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2649982/

37. **De Bresser J, Reijmer YD, van den Berg E, et al.** Utrecht Diabetic Encephalopathy Study Group Microvascular determinants of cognitive decline and brain volume change in elderly patients with type 2 diabetes. Dement Geriatr Cogn Disord. 2010; 30(5):381–386. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20962529

38. **Crane PK, Walker R, Hubbard RA, et al.** Glucose Levels and Risk of Dementia. N Engl J Med. 2013; 369(6):540-548. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3955123/

39. **Badawi A, Klip A, Haddad P, et al.** Type 2 diabetes mellitus and inflammation: Prospects for biomarkers of risk and nutritional intervention. Diabetes Metab Syndr Obes. 2010; 3:173–186. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3047967/

International Journal of Scientific & Engineering Research, Volume 8, Issue 8, August-2017
ISSN 2229-5518