An Association of Virus Infection with Type 2 Diabetes and Alzheimer's Disease

Sajjad Karim[1], Zeenat Mirza[2], Mohammad A. Kamal[2], Adel M. Abuzenadah[2], Esam I. Azhar[2,3], Mohammed H. Al-Qahtani[1] and Sayed S. Sohrab[*,2]

[1]*Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah, Saudi Arabia*

[2]*King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia*

[3]*Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia*

Abstract: Diabetes mellitus type 2 is a metabolic disorder characterized by high blood glucose due to insulin deficiency or resistance. Alzheimer's disease (AD) is a complex neurodegenerative disease leading to irreversible loss of neurons, intellectual abilities, memory and reasoning. The worldwide prevalence of diabetes and AD in elderly population is a major public health concern. Interestingly, both health issues are unraveling the puzzling links. The clinico-pathological relationship between diabetes and AD has been reported at genomic and proteomic levels. The association of virus infection in type 2 diabetes mellitus and AD has been reported in few recent studies, some have shown direct evidence of virus infection in diabetes and AD while other have shown that diabetes increases the risk of developing AD. This review aims to summarize the association of few common viruses like Hepatitis C Virus and Herpes Simplex Virus-1 which affects both these two age-related devastating diseases. We also discuss the pathological links of Influenza virus, Cytomegalovirus, West Nile virus, Enterovirus, Herpes Simplex Virus-2, Hepatitis viruses in diabetes and Influenza virus, Picornavirus and Borna disease virus in AD. Establishing such relationships and defining their common pathogenesis and patho-physiological mechanisms may lead to new concepts and paths for developing novel preventive strategies and pharmacological treatment options for diabetes and AD. This study may aid in future for the identification of a single or a panel of likely blood-based viral biomarkers for early diagnosis of diabetes and AD with high sensitivity and specificity.

Keywords: Type 2 diabetes mellitus, Alzheimer's disease, virus infection, hepatitis virus, herpes simplex virus, influenza virus.

INTRODUCTION

Mammalian aging is an inevitable process associated with a general decline in physiological function and the rapid rise in geriatric populations worldwide is increasing the prevalence of age-related cognitive degenerative disorders such as diabetes and Alzheimer's disease (AD) [1]. Diabetes, with its complications and related diseases, is one of the most chronic, costly and fast-growing health challenges [2]. According to the latest World Health Organization report, 347 million people worldwide suffer from diabetes and will double by 2030 [3, 4]. This disease occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces, which results in hyperglycemia with disturbances of carbohydrate, fat and protein metabolism [5, 6]. There are two main types of diabetes: type 1 and type 2. Type 1 diabetes (T1D) is a chronic autoimmune disease, in which the pancreatic β-cells (which secrete insulin) are selectively destroyed. Inflammatory cytokines, innate and adaptive immune cells, have a role in β-cell damage [7], and type 2 diabetes mellitus (T2DM) is caused due to insufficient insulin production from beta cells [8]. The prevalence of type 2 diabetes have increased markedly over the last 50 years in parallel with obesity, accounting for 85-95% of all diagnosed cases of diabetes [9]. The basis of this metabolic syndrome is insulin resistance (IR) which is defined as an increased requirement for insulin in the peripheral tissues to achieve normal blood glucose levels and to reduce the glucose output in the liver [10]. The symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss [11]. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, nerves and can lead to related complications [4]. There are no specific reasons identified for diabetes. However, life style, particularly obesity is thought to be the primary cause of T2DM in people who are genetically predisposed to the disease. Few links between T2DM and AD have been reported [12-15].

AD, the most important neurodegenerative disease, is irreversible, age-dependent ailment characterized by problems in progressive impairments in memory, language, reasoning, thinking, behavior and visuospatial skills [16]. AD is characterized by two neurotoxic hallmark abnormalities: (1) plaques, extracellular dense deposits of misfolded, aggregated amyloid beta (Aβ) peptide and cellular material that accumulate outside and around nerve cells [17, 18] and (2) neurofibrillary tangles made of twisted tau filaments that build up inside the nerve cells [19]. It is

*Address correspondence to this author at the Special Infectious Agents Unit, King Fahd Medical Research Center, King Abdulaziz University, Post Box No- 80216, Jeddah -21589, Saudi Arabia;
Tel: +966-554627872, +966-640-1000, Ext. 70783; Fax: +966- 6952076;
E-mail: sohrab_sartaj2@rediffmail.com; ssohrab@kau.edu.sa

1996-3181/14 $58.00+.00

the fourth leading cause of death in the western world, one in ten people over 65 and nearly half of those over 85 have AD [20]. In 2010, 36 million people were living with dementia worldwide, and it is estimated to increase up to 66 million by 2030 and 115 million by 2050 [21]. It threatens to become an epidemic if no cure is found, as life expectancy is increasing worldwide. As of 2012, more than 1000 clinical trials have been or are being conducted to find ways to treat this disease, but it is unknown if any of the tested treatments will work [22]. The greatest known risk factor for AD is increasing age followed by family history, environmental factors, which include aluminium, mercury, and viruses but their direct role is under investigation.

Correlations between T2DM and AD have been reported in several epidemiological studies [12, 14, 23, 24]. T2DM has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as vascular dementia (VaD) and AD [25]. So far, no one single factor has been identified as a cause for the development of T2DM or AD. The likely etiology is a combination of factors, including age, genetic inheritance, environmental factors, lifestyle, and viral infections [26-28].

Viral infections constitute risk factor for developing T2DM and AD [29]. Familiar viruses associated with these two diseases are Hepatitis C virus (HCV), Herpes simplex virus (HSV), Influenza Virus (H1N1-serotype), Influenza Virus (H5N1-serotype) Cytomegalovirus (CMV), Enterovirus, West Nile Virus (WNV), Picornavirus and Borna disease virus (BDV). Direct or indirect viral-mediated mechanisms involved in the pathogenesis of T2DM and AD is ambiguous and an area of intensive research. Recent experimental evidences have unraveled many steps involved. However, there are many critical questions whose answers still elude the experimental scientists and we still do not have concrete indications of viruses as culprits responsible for these two age-related devastating health concerns. An understanding of the complex association of virus infection between diabetes and AD is necessary for the design and development of novel drug therapies and lifestyle guidelines aimed at the treatment and/or prevention of these life threatening diseases.

VIRUS INFECTION AS RISK FACTOR FOR T2DM AND AD

Viral infection is one of the most important causes of liver damage, diabetes, neurological disorders and several other diseases world over. The viruses associated with the T2DM and AD are HSV, Hepatitis viruses, CMV, Enterovirus, WNV, Influenza Viruses (H1N1, H5N1 serotypes), Picornavirus and BDV [30, 31] (Fig. **1**).

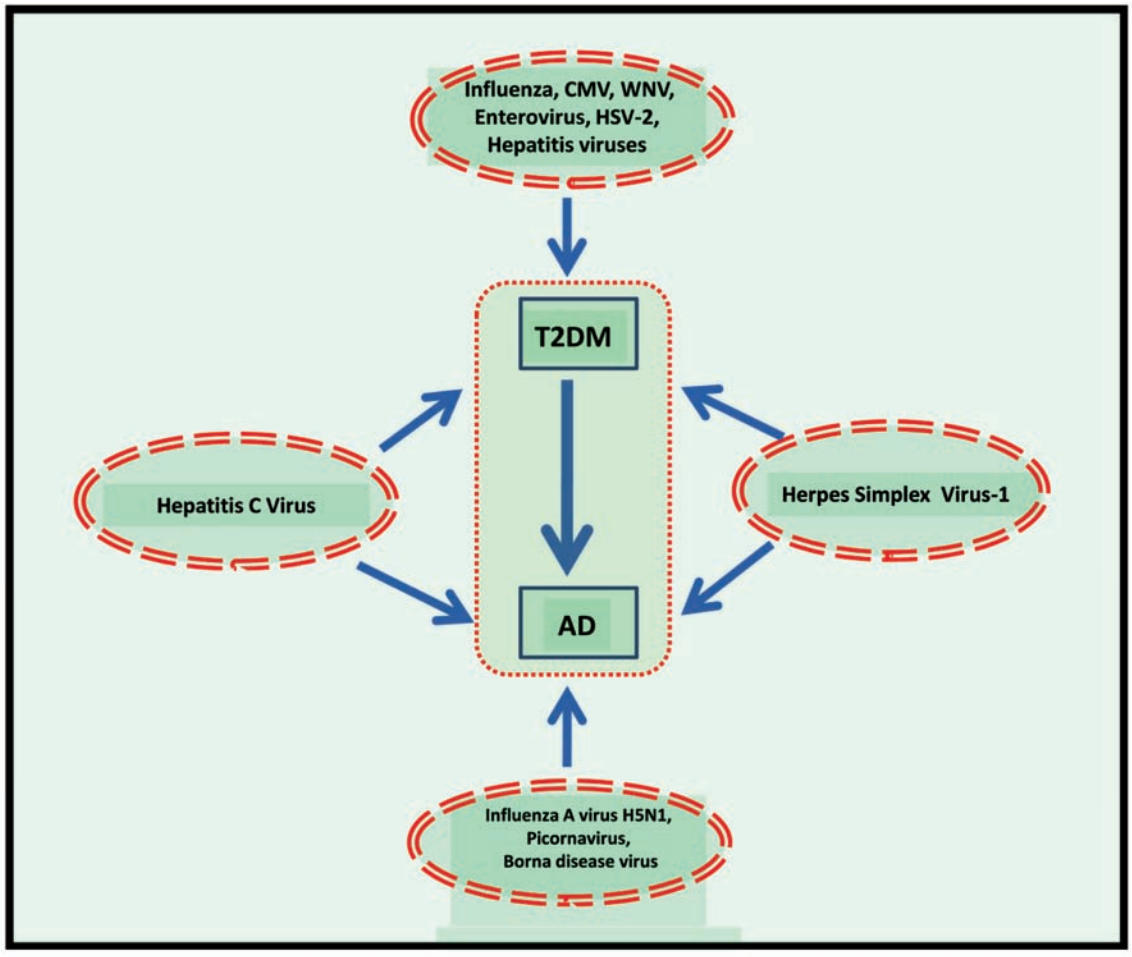

Fig. (1). Schematic diagram showing a link between common virus infection with T2DM and AD. Abbreviations: AD-Alzheimer's Disease, T2DM-Type II Diabetes Mellitus, CMV- Cytomegalovirus, WNV-West Nile Virus, HSV-2-Herpes Simplex virus type-2.

HCV in T2DM

HCV is the most dangerous virus causing liver disease and IR [32]. Nearly 170 million persons worldwide have been infected with the HCV [33]. HCV infection primarily causes liver disease [34], but also has been linked to other conditions including IR and T2DM. The HCV is a blood borne pathogen discovered in 1989, belonging to family *Flavivridae*. HCV infection is one of the most important causes of cirrhosis and hepatocellular carcinoma with significant impact on public health worldwide [35-39]. The HCV genome is 9.6 Kb in size encoding about 3010 amino acids, translated into 10 different structural and non-structural proteins [40-42] (Fig. **2A**). These proteins help in virus replication and affects host cell machinery. In IR, three proteins are involved in particular *i.e*. core protein, NS-3 and NS-5 proteins. The capsid formation takes place by core protein, Helicase and proteolytic activities are controlled by NS-3 protein and down regulation of interferon stimulated genes and RNA polymerase is controlled by NS5-A and NS-5B proteins [43, 44]. HCV infection is directly and/or indirectly affecting the glucose metabolism, leading to IR, and followed by T2DM. Since 1994, several groups have reported an association between HCV infection and T2DM [31, 45-54]. HCV Core protein, NS3 and NS5 proteins, lipogenic and gluconeogenic genes are shown to be involved in IR [55].

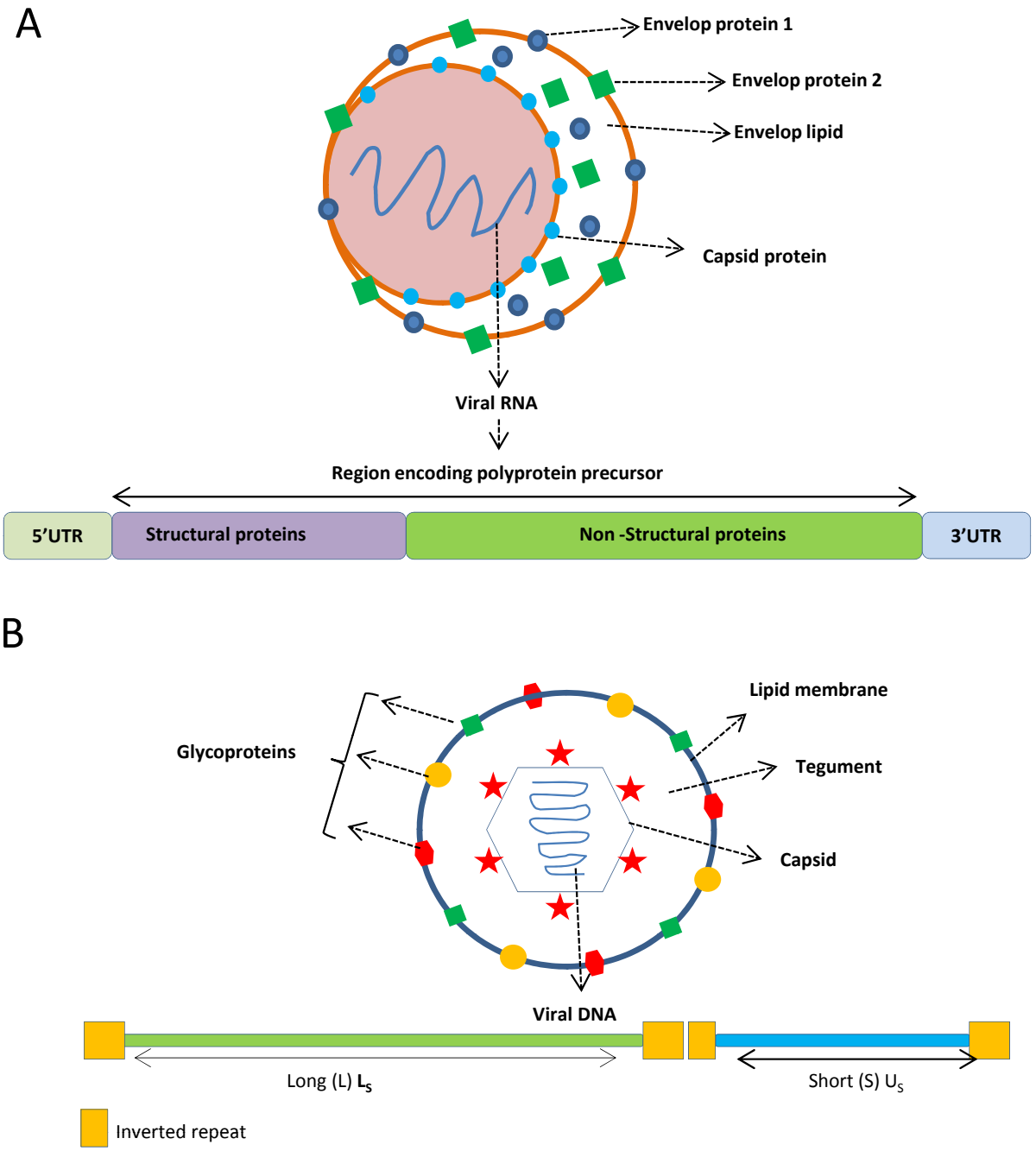

Fig. (2). Model structure and genome map of HCV (**A**) and HSV (**B**).

The epidemiological data clearly indicates a link between chronic hepatitis C (CHC) and disturbed glucose homeostasis. The incidence and increased risk of diabetes is significantly higher in those with hepatitis C-related cirrhosis than those with non- CHC-related cirrhosis [56]. One important survey conducted in general population by Mehta and colleagues, showed a strong link between HCV infection and T2DM [57]. The prevalence of T2DM in CHC ranges from 7.6 to 50%; confounding factors known to influence IR such as viral load, viral genotype, age, body mass index, advanced fibrosis and steatosis likely hence affecting the variation in the prevalence. Since then, various workers have re-confirmed these relationships [52, 58-61]. The HCV induced T2DM in CHC patient ranges from 24-50% and it is five times greater than the other hepatic cirrhosis and its prevalence is increasing gradually [45, 47, 62-70]. An excess risk of T2DM in HCV-infected cases was observed in comparison to HBV infected controls, as both viruses can replicate in extra-hepatic sites and produce β-cell damage resulting in diabetes [71]. In Saudi population, the occurrence of T2DM with chronic liver disease was reported and the prevalence of T2DM patients with CHC was significantly higher than the control (19.2% *vs* 9.2%). The above findings indicate that T2DM is more common in patients with an HCV than non infected individuals [72, 73].

HCV in AD

HCV infection has also shown association with AD [35]. Chronic inflammation is an important cause of AD. Patients with chronic HCV infection may exhibit neuropsychological symptoms and cognitive impairment. Recent evidence suggests that approximately one third of people with chronic HCV experience cognitive impairment. HCV infection increases risk for AD by direct infection in the brain. HCV can cross the blood brain barrier and infect monocytes/macrophages may subsequently cause excessive secretion of cytokines ultimately causing excitotoxicity in the CNS. Microglial activation positively correlated with HCV viraemia and with altered cerebral metabolism [74]. Increased risk for AD was found for participants in their sixties who were infected with HCV. HCV-infected patients who received antiviral therapy have a lower risk for AD. Emerging, intriguing research implicates chronic infection with several pathogenic organisms in the development and progression of AD [30, 75-77].

HCV: A LINK BETWEEN T2DM AND AD

Alzheimer's may Begin in Liver

A recent study reports that AD may originate in liver not brain. Several experimental, clinical and epidemiological data supports that infection with HCV is a leading cause of chronic liver disease [46-49, 55, 78]. The amyloid and plaques, believed to be characteristic of the debilitating AD, starts in the liver rather than in the brain. Sutcliffe and colleagues have indentified three genes (one being PSN-2) in the liver that prevents the formation, accumulation and deposition of amyloid plaques in the mouse's brain [79] suggesting that the therapeutic benefits of a drug in preventing amyloid deposits may not depend on its ability to easily cross the blood-brain barrier but in fighting against its peripheral accumulation.

The HCV infection has been shown to have direct and/or indirect effects on glucose metabolism, leading to IR and in predisposed individuals followed by development of T2DM and AD. The relationship was first reported in 1994 [35]. Since then, various workers have re-confirmed this relationship [47, 50, 52, 58, 60, 61, 80-93]. Based on the reports, it may be hypothesized that the chronic infection in liver and CNS caused by the HCV should be considered as a risk factor for pathogenesis or patho-physiology of T2DM and AD. The reported prevalence of T2DM in CHC patients ranges from 7.6 to 50%; confounding factors known to influence IR are age, body mass index, viral load, viral genotype, advanced fibrosis and steatosis [91].

HSV-1 in T2DM

HSV-1 is the member of Herpes virus family, *Herpesviridae* [34]. The HSV genome is large, double stranded, linear DNA, containing 74 genes and encased within an icosahedral capsid protein, which is covered by an envelope [94, 95] (Fig. **2B**). The clinical and epidemiological studies have demonstrated the direct link between HSV infection and T2DM [88, 96, 97]. Chronic inflammation is involved closely and early on in the pathogenesis of T2DM [98, 99]. The association of HSV-1 infection with T2DM further supported the notion that inflammation and virus infection might be the risk of development of T2DM [88].

HSV-1 in AD

HSV-1 is known to be neurotropic and engages in active transport within neuronal processes. Because HSV enters sensory ganglia (TG or sacral dorsal root nerves) that also project a second process to the CNS, this transport is the more likely route of entry into the brain. The presence of HSV-1 DNA in human brain has been reported by various researchers. A number of investigations have attempted to link various genetic factors, age, and gender to HSV-1 DNA in humans. These reports are somewhat controversial, and in some cases are contradictory. However, there is a general agreement among those who have investigated this area that a large percentage of the human population has HSV-1 DNA in the CNS. During the course of the AD, protein 'plaques' and 'tangles' develop in the structure of the brain, leading to the death of brain cells [100-120].

In AD brains, 90% of the plaques contained the HSV-1 DNA and in aged normal brains, which contain amyloid plaques at a lower frequency, 80% of plaques contained HSV-1 DNA. This shows a strong association of HSV-1 DNA within the amyloid plaques in AD, particularly because most people harbor the virus. Interestingly HSV-1 genome has been amplified in post-mortem brain specimens from numerous AD patients, particularly those who carry the type 4 allele of the gene that encodes apolipoprotein E4, another potential risk factor for AD [121-124]. Indeed, viral infection has been reported to produce molecular hallmarks of neurodegeneration, such as the production and deposit of misfolded protein aggregates, oxidative stress, deficient

autophagic processes, synaptopathies and neuronal death [125].

All of these factors support a viral influence on the development of AD [126, 127]. Four genes, apolipoprotein E4, clusterin, complement receptor 1 and Phosphatidylinositol binding clathrin assembly protein are the main suspects in AD, each of which can be implicated in viral life cycles as well as to amyloid precursor protein and tau and over 100 others implicated in genetic association studies. HSV-1 infection in mice or neuroblastoma cells increases β-amyloid deposition and phosphorylation of the microtubule protein tau. AD-specific tau phosphorylation is induced by HSV-1 [28, 29, 100, 104, 128-133]. HSV-1 induces nuclear accumulation of hyperphosphorylated tau in neuronal cells.

Emerging HSV-1particles interact with APP, the parent protein that, when hydrolyzed, produces the amyloid β that forms the major component of Alzheimer's plaques, and this leads to reduced distribution of APP in HSV-infected cells [86]. Antivirals reduce the formation of key AD molecules in cell cultures acutely infected with HSV-1 [134]. Micro vesicles (L-particles) are secreted from HSV-1 infected cells, offer a highly plausible mechanism for micro vesicular-mediated intracellular communication and also lead to AD by interacting with β-amyloid [135, 136]. The relationship between HSV-1 and AD has been reported *in vivo* and *in vitro* and has moved throughout the brain by axonal transport and play important pathological roles in AD [137]. In a recent study it was reported that specific host miRNA146 is significantly up regulated during HSV-1 infection, this in turn drives the down regulation of complement factor H expression, and induction of AD type pro-inflammatory signaling [128, 138, 139].

HSV-1: A LINK BETWEEN T2DM AND AD

It is reported that most of the T2DM patients die at the age of 70 years approximately due to the cardiovascular complications before AD. The presence of antibodies to HSV-1 is reported to be associated with an increase in the risk of incident myocardial infarction and coronary heart death. HSV-1 has been reported to play a causative role in people carrying the susceptible versions of the apoE gene [129, 140]. This study established a link between T2DM and AD by using two new mouse models and provided further understanding of mechanism. The pathogenesis of AD begins with impaired synaptic function, which results from the accumulation of amyloid-β peptide [141-144]. It is conceivable that insulin actions or their lack may be a link between T2DM and AD [145]. Furthermore, the reduction of brain insulin levels was observed and Akt phosphorylation, a key step in insulin signaling, was severely impaired. These findings provide experimental evidence to support the notion that impairment of insulin signaling might be a mechanistic link between T2DM and AD [140]. In recent years, inflammatory pathways, including that of nuclear factor kappa-light-chain-enhancer of activated B cells, have been linked to metabolic syndrome and neurodegenerative diseases, including AD. As inflammation is often not restricted to central or peripheral tissues or organs, it is tempting to hypothesize that inflammation may be another mechanistic link underlying T2DM and AD [146].

ASSOCIATION OF OTHER VIRAL INFECTIONS IN T2DM AND AD

Several studies have shown that viral infections promote IR, inducing T2DM followed by AD [55, 47]. HCV and HSV-1 infections are found to be directly involved in T2DM and AD; however, viruses below are causing either T2DM or AD: Influenza Virus (H1NI and H5N1 serotypes), Hepatitis Virus (A, B, D, E and F), HSV-2, CMV, WNV, Enterovirus, Picornavirus and BDV.

Influenza A Virus (H1N1)

Influenza A virus, a genus of the *Orthomyxoviridae* family, with 17 different H and 9 different N antigens, causes flu in mammals including humans [147, 148]. Recently it has been reported that Influenza virus infection may play a role as a causative agent of pancreatic damage resulting in hyperlipasemia followed by diabetes in over 50% of subjects [80]. T1D is a chronic autoimmune disease causing selective destruction of insulin-producing β cells and induces T2DM. The non-structural protein 1 of Influenza A viruses has multiple accessory functions, including suppression of innate immunity and adaptive immunity, inhibition of apoptosis and activation of phosphoinositide 3-kinase. Pei and colleagues have shown that intramuscular delivery of non-structural protein 1 of Influenza A (pEGFP-C2/NS1) in mice resulted in reduction in hyperglycemia and diabetes incidence, with an increase in insulin. This result suggests that the expression of non-structural protein 1 is effective for the prevention and treatment of T2DM [149]. Blocking the autoimmune assault of β cells by immune intervention is effective for the prevention and treatment of T1D and T2D.

Influenza A Virus (H5N1)

Like all other influenza virus, the H5N1 is a RNA virus causing disease in humans and other animal species. In 2011, World Health Organization announced the death of 332 people among 566 confirmed human cases infected with H5N1 since 2003 [150]. It has been hypothesized that viruses have an etiological role in the development of several neurodegenerative disorders, reports also suggest that influenza infection might lead to neurotoxic effect causing neurological disorders like Parkinson's and AD [151]. However, role of Influenza virus in AD is still not clear and debatable. Animals infected by H5N1 viruses have demonstrated acute neurological signs ranging from mild encephalitis to motor disturbances to coma. It was observed that any neurotopic Influenza virus that activates the immune system in the brain could contribute by forming protein aggregates leading to CNS disorders [152, 153] and more generally that viruses may be an important etiological agent in AD development. In regions infected by influenza virus (H5N1), the activation of microglia, alpha-synuclein phosphorylation and aggregation persists long after resolution of the infection. It was also observed that the significant loss of dopaminergic neurons in the substantia nigra pars compacta 60 days after infection. The findings suggest that a pandemic H5N1 pathogen, or other neurotropic Influenza virus, could initiate CNS disorders of protein aggregation including AD [154]. Another reports says that amyloid β-peptides which is the major components of neuritic plaques found in AD are aggregated to

fibrillary β -sheet structures (neurotoxic) or form α -helices (membrane poration), which would then trigger cellular death. The 3D NMR structure of Aβ-peptide (1-42) shows two helical regions encompassing residues 8-25 and 28-38, connected by a regular type I beta-turn. The surprising similarity of this structure, as well as the sequence of the C-terminal moiety, with those of the fusion domain of Influenza hemagglutinin suggests a direct mechanism of neurotoxicity leading to AD [155].

HSV-2

Herpes simplex virus-2 is a member of Herpes virus family that infects humans [34]. The presence of antibodies to HSV-2 is reported to be associated with an increase in the risk of incident myocardial infarction and coronary heart diseases. T2D is a major risk factor for cardiovascular morbidity and mortality [88, 156] and is recorded as a coronary artery disease risk equivalent. HSV-2 glycoprotein E is required for efficient virus spread from epithelial cells to neurons and for targeting viral proteins from the neuron cell body into axons [157].

CMV

Cytomegalovirus (CMV) belongs to *Herpesviridae* family and *beta-herpesvirinae* subfamily and its human herpesvirus-5 species is extremely common cause of human infections [34, 158, 159]. Human CMV is found throughout all geographic locations and socioeconomic groups, and infects ~ 40% world population especially elderly people without specific symptoms [160]. Reports have shown that CMV harms cells in the pancreas and predisposing people to T1D and T2D. Due to T1D, immune system becomes weak which favors more susceptibility to infection with CMV and chances of acquiring T2DM becomes 12 times more than the persons who was exposed previously [82, 83].

In fact, CMV is the major viral cause of serious neurological defects in infants, and also a major problem for the immunocompromised. Like other Herpes viruses it can reside latently for long periods in the body and can be reactivated, and it has been suggested that this might be relevant to its putative role in atherosclerosis, AD and (VaD) [107, 114, 161]. VaD is one of the most common causes of dementia after AD [162, 163]. The fact that CMV resides also in some normal brains suggests that if it is a cause of AD, it must be acting in conjunction with another (possibly genetic) factor. Direct role of CMV in AD is not yet established but it is unlikely that CMV is present in brain merely as an opportunistic infection in those who are already HSV-1infected [114, 109, 107]. Recent findings indicate that there is a very strong association between CMV in brain and AD but further studies are needed to reveal whether the virus presence denotes cause or consequence. If it were eventually shown to be a risk factor for AD, there would be the possibility of prevention or of treatment of the disease by vaccination or antiviral therapy, respectively.

HBV

Hepatitis B virus is a member of the *Hepadnavirus* family [164] causes serum hepatitis, an infectious inflammatory illness of the liver [165, 166]. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity. The outer envelope has embedded proteins which are responsible for viral binding and entry into the susceptible cells [167]. The pathogenesis of HCV-associated IR occurs through the inhibition of peroxisome proliferator-activated receptor γ and HBV infection produces the exact opposite effect on peroxisome proliferator-activated receptor γ [47]. The reports on the relationship between T2DM and HBV infection are inconsistent; some workers have found glycemic abnormalities in HBV infected patients while others could not [168]. The association between HBV and the development of hepatic steatosis is also somewhat controversial [169, 170].

Enterovirus

Enteroviruses are members of the *Picornaviridae* family and cause disease in human and mammals. The genome is positive-sense single-stranded RNA approximately 7500 bases [171]. A link between enterovirus infection and diabetes was shown by a study conducted in a group of adults who had been diagnosed with T2DM and compared with those without T2DM. It was observed that forty percent of the pancreas from adults with T2DM contained the enteroviral protein. The incidence of Enterovirus in pancreas of people diagnosed with T2DM was three times higher than in those without it [85].

WNV

WNV belongs to the genus Flavivirus in the family *Flaviviridae*. It is an endemic pathogen found in Africa, Asia, Australia, the Middle East, United States and Europe causing encephalitis [172, 173]. The most important neurological diseases caused by this virus are: west nile encephalitis (brain inflammation), west nile meningitis (Nuroinvasive disease) and meninges inflammation [174]. Important risk factors associated with neuro-invasive disease and West Nile fever includes diabetes mellitus, hypertension, older age and male sex [175]. A recent clinico-epidemiological study supported the association of WNV encephalitis and T2DM but no experimental studies have elucidated the direct role of diabetes in WNV neuropathogenesis [176].

Picornavirus

Picornavirus belongs to the family *Picornaviridae*. Picorna-viruses are non-enveloped with an icosahedral capsid [177] and are important pathogens of humans and animals [94]. The diseases caused by these viruses are varied, ranging from acute "common-cold"-like illnesses, to poliomyelitis, to chronic infections in livestock. This virus-induced memory loss could accumulate over the lifetime of an individual and eventually lead to clinical cognitive memory deficits. However, it is believed that picornoviruses might be having much more common brain effects that are being missed. Clinical studies suggested that picornavirus infections might trigger brain damage by causing inflammation. Brain inflammation is associated with learning and memory loss, and is a key element of AD [178].

BDV

Borna disease virus is a neurotropic RNA virus belongs to family *Bornaviridae* which has a high affinity for the CNS

and causes disease in humans, birds and mammals [179-181]. It has been shown that BDV infection on the CNS impairs synaptic plasticity, which is important for learning and memory [182]. This virus also affects astrocytes, which play a crucial role in the maintenance of homeostasis in the CNS. Infections with BDV reported to contribute to the pathophysiology of AD caused due to the affinity of viral proteins to neurotransmitter receptors which leads to changes in neurotransmission. Based on these reports, chronic infection with several pathogens should be considered a risk factor for sporadic AD. Early intervention against viral infection may delay or even prevent the future development of AD [91, 183, 184].

CONCLUSION AND FUTURE DIRECTION

T2DM is disease of abnormal functioning of pancreas while AD is result of plaques accumulation in brain. Amyloid beta and amylin peptides aggregate together and clumps are found in the Alzheimer's plaques in the neurons of the brain and pancreas; and also found in the pancreas of diabetic patients, and in both diseases their presence has been linked to the disease progression. T2DM and AD are caused by number of factors such as life style, obesity, genetic factors and microbial infection. Virus infection is one of the causative agents and increases the risk of T2DM and AD. It is also established that diabetes increases the risk of AD in later phase of life. Some virus infection directly induces T2DM and/or AD, while other affects indirectly, diabetes is followed by AD. The identification and establishment of viral links involved in T2DM and AD will enable investigators and clinicians to further delineate the pathobiological events leading to AD-related neurodegeneration and complications arising due to diabetes. Knowledge gained from these analyses should facilitate the development of effective strategies for the treatment and prevention of the infection of the involved viral culprits and to exploit the viral genetics and structural information to develop specific vaccines and drugs. To reduce the risk of diabetic patients developing AD, the interactions between the two diseases and intricate molecular mechanism has to be explored. By understanding these interactions, a drug can be developed in future to decrease the risk among T2DM patients of developing AD in later life. Further basic and applied research work will be necessary to reduce, prevent and counteract.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
BDV	=	Borna Disease Virus
CHC	=	Chronic Hepatitis C
CMV	=	Cytomegalovirus
CNS	=	Central Nervous System
HBV	=	Hepatitis B Virus
HCV	=	Hepatitis C Virus
HSV	=	Herpes Simplex Virus
HSV-1	=	Herpes Simplex Virus Type 1
HSV-2	=	Herpes Simplex Virus Type 2
IR	=	Insulin Resistance
T2DM	=	Type 2 Diabetes Mellitus
T1D	=	Type 1 Diabetes
T2D	=	Type 2 Diabetes
VaD	=	Vascular dementia
WNV	=	West Nile Virus

CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest.

ACKNOWLEDGEMENTS

Authors gratefully acknowledge the research facility provided by King Fahd Medical Research Center (KFMRC), King Abdulaziz University, Jeddah, Saudi Arabia. Authors would also like to thank Deanship of Scientific Research (DSR), King Abdulaziz University for providing grant, bearing number: 432/102 for the establishment of state of the art research facilities at KFMRC. We are also thankful to KACST (Strategic award No. 10-BIO1073-03 and 10-BIO1258-03) for grants to establish research facilities at CEGMR, KAU, Jeddah, Saudi Arabia.

REFERENCES

[1] Terry Jr AV, Callahan PM, Hall B, Webster SJ. Alzheimer's Disease and Age-Related Memory Decline(Preclinical). Pharmacol Biochem Behav 2011; 99(2): 190-210.

[2] Hamden K, Jaouadi B, Salami T. Modulatory effect of fenugreek saponins on the activities of intestinal and hepatic disaccharidase and glycogen and liver function of diabetic rats. Biotechnol Bioproc E 2010; 15: 745-53.

[3] Danaei G, Finucane MM, Lu Y, *et al*. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011; 378(9785): 31-40.

[4] WHO: Global status report on noncommunicable diseases 2010. Geneva, World Health Organization, 2011.

[5] Thrower SL, Bingley PJ. What is type 1 diabetes? Medicine 2010; 38: 592-6.

[6] Heydari I, Radi V, Razmjou S. Chronic complications of diabetes mellitus in newly diagnosed patients. Int J Diabet Mellit 2010; 2: 61-3.

[7] Lehuen A, Diana J, Zaccone P. Immune cell crosstalk in type 1 diabetes. Nat Rev Immunol 2010; 10: 501-13.

[8] Kumar V, Fausto N, Abbas AK, Cotran RS, Robbins SL. Robbins and Cotran Pathologic Basis of Disease(7th ed.): Philadelphia, PA, 2005; pp. 1194-5.

[9] Farres J, Albert P, Mireia C, *et al*. Revealing the molecular relationship between type 2 diabetes and the metabolic changes induced by a very-low-carbohydrate low-fat ketogenic diet. Nutr Metab 2010; 7: 88.

[10] Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. Am J Med 2007; 120: 829-34.

[11] Vijan S. Type 2 diabetes. Ann Intern Med 2010; 152(5): ITC3: 1-15.

[12] Haan MN. Therapy Insight: type 2 diabetes mellitus and the risk of late onset Alzheimer's disease. Nat Clin Pract Neurol 2006; 2(3): 159-66.

[13] Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biol Psychiatry 2010; 67: 5050-12.

[14] Priyadarshini M, Kamal MA, Greig NH, *et al*. Alzheimer's disease and type 2 diabetes: exploring the association to obesity and tyrosine hydroxylase. CNS Neurol Disord Drug Targets 2012; 11(4): 482-9.

[15] Biophysical society. 2013; February 1. Type II diabetes and Alzheimer's connection. Science Daily. Available from: http: //www.sciencedaily.com-/releases/2013/02/130201095945.htm

[16] Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. Neurobiol Aging 1998; 19(3): 173-89.

[17] Wolfe MS. Secretase Targets for Alzheimer's Disease: Identification and Therapeutic Potential. J Med Chem 2001; 44: 2039-60.

[18] Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 2001; 81: 741-66.

[19] Nunan J, Williamson NA, Hill AF, *et al*. Proteasome-mediated degradation of the C-terminus of the Alzheimer's disease beta-amyloid protein precursor: effect of C-terminaltruncation on production of beta-amyloid protein. J Neurosci Res 2003; 74: 378-85.

[20] Brookmeyer R, Johnson E, Ziegler GK, Arrighi MH. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007; 3(3): 186-91.

[21] World Alzheimer's Report, 2012: Available form: http: //www.alz.co.uk/research/WorldAlzheimerReport

[22] Clinical Trials. Found 1012. Studies with search of: Alzheimer". US National Institutes of Health. Retrieved 01-10-2011.

[23] Luchsinger JA. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004; 63(7): 1187-92.

[24] Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med 2004; 82(8): 510-29.

[25] Pasquier F. Diabetes and cognitive impairment: how to evaluate the cognitive status?. Diabetes Metab 2010; 36(Suppl 3): S100-5.

[26] Shoback D, David GG. Greenspan's basic & clinical endocrinology. 9th ed. McGraw-Hill Medical, New York, 2011; p. 14.

[27] Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Phys 2009; 79(1): 29-36.

[28] Riserus U, Willett WC, Hu FB. Dietary fats and prevention of type 2 diabetes. Prog Lipid Res 2009; 48(1): 44-51.

[29] Carter CJ. Alzheimer's Disease: A Pathogenetic Autoimmune Disorder Caused by Herpes Simplex in a Gene-Dependent Manner. Int J Alzheimers Dis 2010a; 140539.

[30] Carter CJ. Familial and late-onset Alzheimer's disease: Evidence for an auto-immune component triggered by viral, microbial and allergen antigens with homology to beta-amyloid and APP mutant peptides. Nat Preced 2010b; 1: 4662.

[31] Cadranel JF, Di Martino V, Lambrey G, *et al*. Prevalence of hepatitis C infection and risk factors in hospitalized diabetic patients: results of a cross-sectional study. Eur J Gastroenterol Hepatol 2008; 20: 829-36.

[32] Dienstang JL, Isselbacher KJ. Acute viral hepatitis. In: Kasper DL, Braunwald E, Fauci AS, Eds. Harrison's Principles of Internal Medicine; 16th edn.; McGraw-Hill, New York 2005; pp.1825-55.

[33] Alter MJ, Kruszon MD, Nainan OV, *et al*. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999; 341: 556-62.

[34] Ryan KJ, Ray CG. Sherris Medical Microbiology; 4th edn.; McGraw Hill; New york 2004; pp. 566-9.

[35] Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. J Hepatol 1994; 21: 1135-9.

[36] Miura K, Taura K, Kodama Y, Schnabl B, Brenner DA. Hepatitis C virus induced oxidative stress suppresses hepcidin expression through increased histone deacetylase activity. Vir Hepat 2008; 48(5): 1420-9.

[37] Joyce MA, Walters KA, Lamb SE, *et al*. HCV Induces Oxidative and ER Stress, and Sensitizes Infected Cells to Apoptosis in SCID/Alb-uPA Mice. PLoS Pathog 2009; 5(2): e1000291.

[38] Clement S, Pascarella S, Negro F. Hepatitis C Virus Infection: Molecular Pathways to steatosis, Insulin resistance and oxidative stress. Virus 2009; 1: 126-43.

[39] Zein CO, Levy C, Basu A, Zein NN. Chronic hepatitis C and type II diabetes mellitus: a prospective cross-sectional study. Am J Gastroenterol 2005; 100: 48-55.

[40] Choo QL, Kuo G, Weiner AJ, *et al*. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244(4902): 359-62.

[41] Bartenschlager R, Lohmann V. Replication of the hepatitis C virus. Baillieres Best Pract Res Clin Gastroenterol 2000; 14: 241-54.

[42] Bartenschlager R, Frese M, Pietschmann T. Novel insights into hepatitis C virus replication and persistence. Adv Virus Res 2004; 63: 71-180.

[43] Gale MJ, Blakely SM, Kwieciszewski B, *et al*. Hepatitis C virus non-structural 5a protein. Mol Cell Biol 1998; 18: 5208-18.

[44] Miyamoto H, Moriishi K, Moriya K, *et al*. Involvement of the PA28 Dependent Pathway inInsulin Resistance induced by Hepatitis C Virus Core Protein. J Virol 2007; 81(4): 1727-35.

[45] Younossi ZM, Stepanova M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiac outcomes. Aliment Pharmacol Ther 2013; 37: 647-52.

[46] Solomon A, Solomon A, Adane M, Tamrat A. Association of Hepatitis C Virus Infection with Type II Diabetes in Ethiopia: A Hospital-Based Case-Control Study. Interdisciplin Persp Infect Dis 2012; 7: 354656.

[47] Gutierrez YG, Gadalupe PRM, Nahum MS. Viral hepatitis infection and insulin resistance: A review of the pathophysiological mechanisms. Salud Pública Mex 2011; 53 (1): S46-51.

[48] Saxena AK, Suresh RB. An intriguing relationship between type 2 diabetes mellitus and hepatitis C virus infection: the renal perspective. Hepat Monthly 2009; 9(2): 89-91.

[49] Fabrizi FP, Lampertico G, Lunghi S, Mangano F, Aucella PM. Review article: hepatitis C virus infection and type-2 diabetes mellitus in renal diseases and transplantation. Aliment Pharmacol Ther 2005; 21: 623-32.

[50] Mehta SH, Brancati FL, Strathdee SA, *et al*. Hepatitis C virus infection and incident type 2 diabetes. Hepatology 2003; 38: 50-6.

[51] Negro F, Alaei M. Hepatitis C virus and type 2 diabetes. World J Gastroenterol 2009; 15: 1537-47.

[52] Mason AL, Lau JY, Hoang N, *et al*. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999; 29: 328-33.

[53] Simon R, Hernandez C, Genesca J, Jardi R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. Diabetes Care 1996; 19: 998-1000.

[54] Venessa P, Jenny H. Hepatitis C and diabetes: one treatment for two diseases? Liver Int 2010; 30(3): 356-64.

[55] Parvaiz F, Sobia M, Huma T, *et al*. Hepatitis C Virus Infection: Molecular Pathways to Insulin resistance. Virol J 2011; 8: 474.

[56] Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. Mayo Clin Proc 2000; 75: 355-9.

[57] Mehta SH, Brancati FL, Sulkowski MS, *et al*. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med 2000; 133: 592-9.

[58] Moucari R, Asselah T, Cazals-Hatem D. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4: serum HCV RNA level, and liver fibrosis. Gastroenterology 2008; 134: 416-23.

[59] Kamal MA, Tan Y, Seale JP, Qu X. Targeting BuChE-inflammatory pathway by SK0506 to manage type 2 diabetes and Alzheimer disease. Neurochem Res 2009; 34(12): 2163-9.

[60] Caronia S, Taylor K, Pagliaro L, *et al*. Further evidence for an association between noninsulin- dependent diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999; 30: 1059-63.

[61] Grimbert S, Valensi P, Levy MC. High prevalence of diabetes mellitus in patients with chronic hepatitis C. A case-control study. Gastroenterol Clin Biol 1996; 20: 544-8.

[62] Vincent W, Wang S. Hepatitis C virus infection and diabetes: Not a straight forward relationship. J Gastroenterol Hepatol 2012; 27: 1688-94.

[63] White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. J Hepatol 2008; 49: 831-44.

[64] Cho N, Joon WM, Syed IA, Mala M. Relationship between hepatitis C virus infection and type 2 diabetes mellitus: Meta-analysis. World J Gastroenterol 2012; 18(14): 1642-51.

[65] Rouabhia S, Rachid M, Hocine B, *et al*. Prevalence of type 2 diabetes in Algerian patients with hepatitis C virus infection. World J Gastroenterol 2010; 16(27): 3427-31.

[66] Romero-Gomez M. Insulin resistance and hepatitis C. World J Gastroenterol 2006; 12: 7075-80.

[67] Arao M, Murase K, Kusakabe A, *et al*. Prevalence of diabetes mellitus in Japanese patients infected chronically with hepatitis C virus. J Gastroenterol 2003; 38: 355-60.

[68] Waki K, Noda M, Sasaki S, *et al*. JPHC Study Group. Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population based prospective study in the JPHC study cohort I. Diabet Med 2005; 22: 323-31.

[69] Ozylkan E, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. Am J Gastroenterol 1996; 91: 1480-1.

[70] Parolin MB, Rea R, Vargas RM, *et al*. Prevalence of hepatitis C infection in patients with type 2 diabetes mellitus. Arq Gastroenterol 2006; 43: 77-80.

[71] Naing CJ, Wah M, Syed IA, Mala M. Relationship between hepatitis C virus infection and type 2 diabetes mellitus: Meta-analysis. World J Gastroenterol 2012; 18(14): 1642-51.

[72] Singhal AK, Ayoola AE. Prevelance and factors affecting occurrence of type 2 diabetes mellitus in saudi patients with chronic liver disease. Saudi J Gastroenterol 2008; 14(3): 118-21.

[73] Akbar DH, Siddique AM, Ahmed MM. Prevalence of Type-2 diabetes in patients with hepatitis C and B virus infection in Jeddah, Saudi Arabia. Med Princ Pract 2002; 11(2): 82-5.

[74] Chiu SL, Chen CM, Cline HT. Insulin receptor signaling regulates synapse number, dendritic plasticity, and circuit function *in vivo*. Neuron 2008; 58: 708-19.

[75] Zhang C, Cai Z, Kim YC, *et al*. Stimulation of hepatitis C virus(HCV) nonstructural protein 3(NS3) helicase activity by the NS3 protease domain and by HCV RNA-dependent RNA polymerase. J Virol 2005; 79: 8687-97.

[76] Deans E. Nutrition and Alzheimer's Disease-Dangers of Insulin Resistance and Low Cholesterol. Evol Psychiatry 2011; 1.

[77] Miklossy J. Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation 2011; 8: 90.

[78] Shintani YH, Fujie HM. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology 2004; 126(3): 840-8.

[79] Sutcliffe JG, Hedlund PB, Thomas EA, Bloom FE, Hilbush BS. Peripheral reduction of beta-amyloid is sufficient to reduce brain beta-amyloid: implications for Alzheimer's disease. J Neurosci Res 2011; 89: 808-14.

[80] Capua I, Mercalli A, Pizzuto MS, *et al*. Influenza A viruses grow in human pancreatic cells and cause pancreatitis and diabetes in an animal model. J Virol 2013; 87(1): 597-610.

[81] Arase Y, Mariko K, Fumitaka S, *et al*. Effect of Type 2 Diabetes on Risk for Malignancies Includes Hepatocellular Carcinoma in Chronic Hepatitis C. Hepatology 2013; 57(3): 964-73.

[82] Rachael R. Type 2 diabetes linked to common virus. My Health News Daily 2012; p. 1.

[83] Sarah S. Could a Common Virus Lead to Type 2 Diabetes in Seniors? My Health News Daily 2012; p.1

[84] Huang JF, Yu ML, Dai CY, Chuang WL. Glucose abnormalities in hepatitis C virus infection. Kaohsiung J Med Sci 2013; 29(2): 61-8.

[85] Richardson SJ, Willcox A, Bone AJ. The prevalence of enteroviral capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. Diabetologia 2009; 52(6): 1143-51.

[86] Cheng SB, Ferland P, Webster P, Bearer EL. Herpes simplex virus dances with amyloid precursor protein while exiting the cell. PLoS One 2011; 6(3): e17966.

[87] Negro F. Mechanisms of hepatitis C virus-related insulin resistance. Clin Res Hepatol Gastroenterol 2011; 35(5): 358-63.

[88] Yuhua S, Weidong P, Yongjian Wu, Yuejin Y. An Association of Herpes Simplex Virus Type 1 Infection With Type 2 Diabetes. Diabetes Care 2005; 28: 2.

[89] Roberts BW, Cech I. Association of type 2 diabetes mellitus and seroprevalence for cytomegalovirus. South Med J 2005; 98(7): 686-92.

[90] Letenneur L, Peres K, Fleury H, *et al*. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PLoS ONE 2008; 3(11): e3637.

[91] Honjo K, van Reekum R, Verhoeff NP. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? Alzheimers Dement 2009; 5(4): 348-60.

[92] Dobson CB, Itzhaki RF. Herpes simplex virus type 1 and Alzheimer's disease. Neurobiol Aging 1999; 20(4): 457-65.

[93] Pyles RB. The association of herpes simplex virus and Alzheimer's disease: a potential synthesis of genetic and environmental factors (PDF). Herpes 2001; 8(3): 64-8.

[94] Mettenleiter TC, Klupp BG, Granzow H. Herpesvirus assembly: a tale of two membranes. Curr Opin Microbiol 2006; 9(4): 423-9.

[95] McGeoch DJ, Rixon FJ, Davison AJ. Topics in herpesvirus genomics and evolution. Virus Res 2006; 117(1): 90-104.

[96] Ott A. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999; 53: 1937-42.

[97] Kroner, Z. The relationship between Alzheimer's disease and diabetes: Type 3 diabetes? Altern Med Rev 2009; 14: 373-9.

[98] Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004; 27: 813-23.

[99] Helmersson J, Vessby B, Larsson A, Basu S. Association of type 2 diabetes with cycloxygenase-mediated inflammation and oxidative stress in an elderly population. Circulation 2004; 109: 1729-34.

[100] Wozniak MA, Frost AL, Itzhaki RF. Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. J Alzheimers Dis 2009; 16(2): 341-50.

[101] Hill JM, Ball MJ, Neumann DM. The high prevalence of herpes simplex virus type 1 DNA in human trigeminal ganglia is not a function of age or gender. J Virol 2008; 82(16): 8230-4.

[102] Carter CJ. Interactions between the products of the Herpes simplex genome and Alzheimer's disease susceptibility genes: relevance to pathological-signalling cascades. Neurochem Int 2008; 52(6): 920-34.

[103] Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF. Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. J Med Virol 2005; 75: 300-6.

[104] Itzhaki RF, Dobson CB, Wozniak MA. Herpes simplex virus type 1and Alzheimer's disease. Ann Neurol 2004; 55: 299-300.

[105] Hemling N, Roytta M, Rinne J, *et al*. Herpes viruses in brains in Alzheimer's and Parkinson's diseases. Ann Neurol 2003; 54: 267-71.

[106] Wozniak MA, Mee AP, Itzhaki RF. Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol 2009; 217: 131-8.

[107] Lin WR, Wozniak MA, Cooper RJ, Wilcock GK, Itzhaki RF. Herpes viruses in brain and Alzheimer's disease. J Pathol 2002; 197: 395-402.

[108] Liedtke W, Opalka B, Zimmermann CW, Lignitz E. Age distribution of latent herpes simplex virus 1 and varicella-zoster virus genome in human nervous tissue. J Neurol Sci 1993; 116: 6-11.

[109] Lin WR, Graham J, MacGowan SM, Wilcock GK, Itzhaki R. Alzheimer's disease, herpes virus in brain, apolipoprotein E4 and herpes labialis. Alzheimer Rep 1998; 1: 173-8.

[110] Lin WR, Wozniak MA, Wilcock GK, Itzhaki RF. Cytomegalovirus Is Present in a Very High Proportion of Brains from Vascular Dementia Patients. Neurobiol Dis 2002; 9: 82-7.

[111] Beffert U, Bertrand P, Champagne D, Gauthier S, Poirier J. HSV-1 in brain and risk of Alzheimer's disease. Lancet 1998; 351: 1330-1.

[112] Itzhaki RF, Lin WR. Herpes simplex virus type I in brain and the type 4allele of the apolipoprotein E gene are a combined risk factor for Alzheimer's disease. Biochem Soc Trans 1998; 26: 273-7.

[113] Sanders VJ, Felisan SL, Waddell AE, *et al*. Presence of herpes simplex DNA in surgical tissue from human epileptic seizure foci detected by polymerase chain reaction: Preliminary study. Arch Neurol 1997; 54: 954-60.

[114] Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet 1997; 349: 241-4.

[115] Sanders VJ, Felisan S, Waddell A, Tourtellotte AA. Detection of herpes virus in postmortem multiple sclerosis brain tissue and controls by polymerase chain reaction. J Neuro Virol 1996; 2: 249-58.

[116] Itzhaki RF, Maitland NJ, Wilcock GK, Yates CM, Jamieson GA. Detection by polymerase chain reaction of herpes simplex virus type1(HSV1) DNA in brain of aged normals and Alzheimer's disease patients. In: Corain B, Iqbal K, Nicolini M, *et al*., Eds.; Alzheimer's disease: Advances in clinical and basic research. Chichester, UK, John Wiley & Sons 1993; pp. 97-102.

[117] Bertrand P, Guillaume D, Hellauer K, *et al*. Distribution of Herpes simplex virus type 1 DNA in selected areas of normal and Alzheimer's disease brains: A PCR study. Neurodegeneration 1993; 2: 201-8.

[118] Nicoll JA, Love S, Kinrade E. Distribution of herpes simplex virus DNA in the brains of human long-term survivors of encephalitis. Neurosci Lett 1993; 157: 215-8.

[119] Jamieson GA, Maitland NJ, Craske J, Wilcock GK, Itzhaki RF. Detection of herpes simplex virus type 1 DNA sequences in normal and Alzheimer's disease brain using polymerase chain reaction. Biochem Soc Trans 1991; 19: 122S.

[120] Jamieson GA, Maitland NJ, Wilcock K, Yates CM, Itzhaki RF. Herpes simplex virus type 1 DNA is present in specific regions of brain from aged people with and without senile dementia of the Alzheimer type. J Pathol 1992; 167: 365-8.

[121] Xu F, Sternberg MR, Kottiri BJ. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA 2006; 296(8): 964-73.

[122] Xu F, Lee FK, Morrow RA. Seroprevalence of herpes simplex virus type 1 in children in the United States. J Pediatr 2007; 151(4): 374-7.

[123] Peter JB, Sevall JS. Review of 3200 serially received CSF samples submitted for type-specific HSV detection by PCR in the reference laboratory setting. Mol Cell Probes 2001; 15(3): 177-82.

[124] Ball MJ, Mathews R, Steiner I. Latent HSV 1 virus in trigeminal ganglia: the optimal site forlinking prevention of Alzheimer's disease to vaccination. Neurobiol Aging 2001; 22(5): 705-9.

[125] Chiara GD, Maria EM, Rossella S, *et al*. Infectious Agents and Neurodegeneration. Mol Neurobiol 2012; 46: 614-38.

[126] Toma HS, Murina AT, Areaux RG Jr, *et al.* Ocular HSV-1 latency, reactivation and recurrent disease. Sem Ophthalmol 2008; 23: 249-73.

[127] Al-Dujaili LJ, Clerkin PP, Clement C, *et al*. Ocular herpes simplex virus: How are latency, reactivation, recurrent disease and therapy interrelated? Future Microbiol 2011; 6: 877-907.

[128] Ball MJ, Lukiw WJ, Kammerman EM, Hill JM. Intracerebral propagation of Alzheimer's disease: strengthening evidence of a herpes simplex virus etiology. Alzheimers Dement 2012; (12): 1552-5260.

[129] Itzhaki RF, Wozniak MA. Alzheimer's disease-like changes in herpes simplex virus type 1 infected cells: the case for antiviral therapy, Rejuvenation Res 2008a; 11(2): 319-20.

[130] Itzhaki RF, Wozniak MA. Herpes simplex virus type 1 in Alzheimer's disease: the enemy within. J Alzheimers Dis 2008 b; 13(4): 393-405.

[131] Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB. Herpes simplex virus infection causes cellular β -amyloid accumulation and secretase upregulation. Neurosci Lett 2007; 429(2-3): 95-100.

[132] Itzhaki RF, Dobson CB, Lin WR, Wozniak MA. Association of HSV1 and apolipoprotein E-ε4 in Alzheimer's disease. J NeuroVirol 2001; 7(6): 570-1.

[133] Alvarez G, Aldudo J, Alonso M, Santana S, Valdivieso F. Herpes simplex virus type 1 induces nuclear accumulation of hyperphosphorylated tau in neuronal cells. J Neurosci Res 2012; 90: 1020-9.

[134] Wozniak MA, Frost AL, Preston CM, Itzhaki RF. Antivirals reduce the formation of key Alzheimer's disease molecules in cell cultures acutely infected with herpes simplex virus type 1. PLoS One 2011; 6(10): e25152.

[135] Kammerman EM, Neumann DM, Ball MJ, Lukiw W, Hill JM. Senile plaques in Alzheimer's disease brains: Possible association of beta amyloid with herpes simplex virus type 1(HSV-1) L-particles. Med Hypotheses 2006; 66: 294-9.

[136] Meckes DG Jr, Raab TN. Microvesicles and viral infection. J Virol 2011; 85: 12844-54.

[137] Bearer EL. HSV, axonal transport and Alzheimer's disease: *in vitro* and *in vivo* evidence for causal relationships. Fut Virol 2012; 7(9): 885-99.

[138] Li YY, Cui JG, Hill JM, *et al*. Increased expression of miRNA-146a in Alzheimer's disease transgenic mouse models. Neurosci Lett 2011; 487: 94-8.

[139] Lukiw WJ, Cui JG, Yuan LY, *et al.* Acyclovir or A[beta]42 peptides attenuate HSV-1-induced miRNA-146a levels in human primary brain cells. Neuro Report 2010; 21: 922-7.

[140] Takeda S. Diabetes accelerated memory dysfunction *via* cerebrovascular inflammation and Aβ deposition in Alzheimer mouse model with diabetes. Proc Natl Acad Sci USA 2010; 107: 7036-41.

[141] Selkoe DJ. Alzheimer's disease is a synaptic failure. Science 2002; 298: 789-91.

[142] Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in Alzheimer's disease. Neuron 2004; 44: 181-93.

[143] Zhang C. Presenilins are essential for regulating neurotransmitter release. Nature 2009; 460: 632-6.

[144] Klein WL. Synaptic targeting by Aβ oligomers(ADDLS) as a basis for memory loss in early Alzheimer's disease. Alzheimers Dement 2006; 2: 43-55.

[145] Steen E. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease—is this type 3 diabetes? J Alzheimers Dis 2005; 7: 63-80.

[146] Weiping Han, Cai Li. Linking type 2 diabetes and Alzheimer's disease. PNAS 2010; 107(15): 6557-8.

[147] Gewin V. Bats harbour influenza. Nature News 2012. Available from: http://www.nature.com/news/bats-harbour-influenza-1.10112

[148] Tong S, Li Y, Rivailler P, *et al*. A distinct lineage of influenza a virus from bats. Proc Natl Acad Sci USA 2012; 109(11): 4269-74.

[149] Pei D, Dai J, Kuang Y, *et al*. Effect of influenza A virus non-structural protein 1(NS1) on a mouse model of diabetes mellitus induced by Streptozotocin. Biochem Biophys Res Commun 2012; 419(1): 120-5.

[150] WHO 2013. Cumulative Number of Confirmed Human Cases for Avian Influenza A/(H5N1) Reported to WHO, 2003-2011.

[151] Mattson MP. Infectious agents and age-related neurodegenerative disorders. Ageing Res Rev 2004; 3: 105-20.

[152] Jellinger KA. Neuropathological aspects of Alzheimer disease, Parkinson disease and frontotemporal dementia. Neurodegener Dis 2008; 5: 118-21.

[153] Tansey MG, Frank-Cannon TC, McCoy MK, *et al*. Neuroinflammation in Parkinson's disease: Is there sufficient evidence for mechanism-based interventional therapy? Front Biosci 2008; 1(13): 709-17.

[154] Haeman Janga, David B, Katharine SR, *et al*. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proc Natl Acad Sci USA 2009; 106(33): 14063-8.

[155] Crescenzi O, Tomaselli S, Guerrini R, *et al*. Solution structure of the Alzheimer amyloid β -peptide(1-42) in an apolar microenvironment. Similarity with a virus fusion domain. Eur J Biochem 2002; 269(22): 5642-8.

[156] Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease. Pathophysiology, clinical consequences, and medical therapy: part II. Circulation 2003; 108: 1655-61.

[157] Wang F, Zumbrun EE, Huang J, *et al*. Herpes simplex virus type 2 glycoprotein E is required for efficient virus spread from epithelial cells to neurons and for targeting viral proteins from the neuron cell body into axons. Virology 2010; 405(2): 269-79.

[158] Koichi Y, Arvin AM, Gabriella C, *et al*. Human herpesviruses: biology, therapy, and immunoprophylaxis. Cambridge, UK: Cambridge University Press 2007.

[159] Sweet C. The pathogenicity of cytomegalovirus. FEMS Microbiol Rev 1999; 23(4): 457-82.

[160] Offermanns S, Rosenthal W. Encyclopedia of Molecular Pharmacology. 2nd edn.; Springer 2008; pp. 437-8.

[161] Kol A, Libby P. The mechanisms by which infectious agents may contribute to atherosclerosis and its clinical manifestations. Trends Cardiovasc Med 1998; 8: 191-9.

[162] Nyenhuis DL, Gorelick PB. Vascular dementia: a contemporary review of epidemiology, diagnosis, prevention, and treatment. J Am Geriatr Soc 1998; 46(11): 1437-48.

[163] Arvanitakis Z, Hachinski V. Vascular Cognitive Impairment: What Else Do We Need to Learn? In: Terry RD, Katzman R, Bick KL, Sisodia SS., Eds., Alzheimer Disease; 2nd edn.; Philadelphia: Lippincott Williams and Wilkins 2000.

[164] Zuckerman AJ. Hepatitis Viruses. In: Baron S, *et al*. Baron's Medical Microbiology. 4th ed. University of Texas Medical Branch 1996.

[165] Te H, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. Clin Liv Dis 2010; 14(1): 1-21.

[166] Locarnini S. Molecular virology of hepatitis B virus. Semin Liver Dis 2004; 24(Suppl 1): 3-10.

[167] Kay A, Zoulim F. Hepatitis B virus genetic variability and evolution. Virus Res 2007; 127(2): 164-76.

[168] Custro N, Carroccio A, Ganci A. Glycemic homeostasis in chronic viral hepatitis and liver cirrhosis. Diabetes Metab 2001; 1: 476-81.

[169] Wang CC, Hsu CS, Liu CJ. Association of chronic hepatitis B virus infection with insulin resistance and hepatic steatosis. J Gastroenterol Hepatol 2008; 23: 779-82.

[170] Kim KH, Shin HJ, Kim K. Hepatitis B virus X protein induces hepatic steatosis *via* transcriptional activation of SREBP1 and PPAR gamma. Gastroenterol 2007; 132: 1955-67.

[171] Li L, He Y, Yang H. Genetic Characteristics of Human Enterovirus 71 and Coxsackievirus A16 Circulating from 1999 to 2004 in

Shenzhen, People's Republic of China. J Clin Microbiol 2005; 43(8): 3835-9.

[172] Nash D, Mostashari F. The outbreak of west nile virus infection in the New York city area in 1999. NEJM 2001; 344(24): 1807-12.

[173] Anticona EM, Zainah H, Ouellette DR. Two Case Reports of Neuroinvasive West Nile Virus Infection in the Critical Care Unit. Case Rep Infect Dis Vol 2012; 2012: 839458.

[174] Davis LE, DeBiasi R, Goade DE. West Nile virus neuroinvasive disease. Ann Neurol 2006; 60(3): 286-300.

[175] Jean CM, Honarmand S, Louie JK, Glaser CA. Risk factors for West Nile virus neuroinvasive disease, California, 2005. Emerg Infect Dis 2007; 12: 1918-20.

[176] Kumar M, Roe K, Nerurkar PV, *et al*. Impaired virus clearance, compromised immune response and increased mortality in type 2 diabetic mice infected with West Nile virus. PLoS One 2012; 7(8): e44682.

[177] Martinez ES, Saiz M, Sobrino F. Foot-and- Charles H. Alzheimer's disease linked to the common cold. Mouth Disease Virus. Animal Viruses Mol Biol 2008; 22-6.

[178] Charles, H. Alzheimer's disease linked to the common cold. Mail Online 2006; p:1. http://www.dailymail.co.uk/health/article-412145/Alzheimers-disease-linked-common-cold.html

[179] Durrwald R, Ludwig H. Borna Disease Virus(BDV): a(Zoonotic?) WorlwidePathogen. A Review of the History of the Disease and the Virus Infection with Comprehensive Bibliography. J Vet Med 1997; 44(3): 147-84.

[180] Ludwig H, Bode L. Borna Disease Virus: new aspects on infection, disease, diagnosis and epidemiology. Rev Sci Tech Off Int Epiz 2000; 19(1): 259-88.

[181] Rott R, Herzog S, Fleischer B, Winokur A, Amsterdam J, Dyson W, Koprowski H. Detection of serum antibodies to Borna Disease Virus in patients with psychiatric disorders. Science 1985; 228(4700): 755-756.

[182] Volmer R, Prat CMA, Masson G, Garenne A, Gonzales-Dunia.; D. Borna Disease Virus Infection Impairs Synaptic Plasticity. J Virol 2007; 81(16): 8833-8837.

[183] Solbrig MV. Animal models of CNS viral disease: Examples from Borna disease virus models. Interdiscip Perspect Infect Dis 2010; (709791): 1-6.

[184] Sylva R, Lubos J. Borna disease virus and Psychiatric Disorders: Can Viruses Influence Psychiatric Disorders? Psychiatric Disord Worldwide Adv 2011; 307-833-5.

Received: March 24, 2013 **Revised: April 6, 2013** **Accepted: April 8, 2013**