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Determination of Proteomics Correlation between Type 2 Diabetes Mellitus and Parkinson's disease

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Abstract

The etiology of Type 2 Diabetes Mellitus (T2DM) and Parkinson's disease (PD) is very different, however these two diseases are linked with each other as the Patients suffering from diabetes have 40% more risk for getting Parkinson's disease as compared to diabetes free individuals. In this review article, the dysregulation of some important proteins has been revealed, having distinct association in the pathophysiological mechanisms of T2DM and PD such as protein misfolding and aggregation, autophagy dysregulation, mitochondrial damage (dysfunction), Endoplasmic reticulum stress (malfunction), inflammation and loss of central and peripheral synapse. The proteins involved in the pathogenesis of T2DM and PD through different pathophysiological pathways are amyloid fibres, Parkin & PINK1, Beclin, ATG7, LC3-II, Carnosinase (CNDP2), Synaptophysin, SNAP-25, Sorcin, GLP-1 analogues, AMPK and ADH1A1. Dysregulation of these proteins leads to the pathogenesis of both diseases. In conclusion, the current study suggests that type 2 diabetes mellitus and Parkinson's disease are associated through number of common proteins and Pathophysiological pathways but it is too earlier to conclude that T2DM is a risk factor for the progression of PD. Further studies are required to reveal the relationship of T2DM with PD.

Key words: Type 2 Diabetes Mellitus, Parkinson's disease, Substantia nigra and Proteomics.

1. INTRODUCTION

1.1 Type 2 Diabetes Mellitus (T2DM)

Type 2 Diabetes Mellitus (T2DM) is a complicated and developing disorder characterized by diverse metabolic deficiencies, affecting many organs (Wu et al., 2014). T2DM is caused by combination of genetic, environmental and behavioral factors (Chen et al., 2011; Diabetes mellitus interagency coordinating committee [DMICC], 2011). The lifestyle factors identified to develop T2DM are lack of exercise, inactive lifestyle, smoking and excessive alcohol drinking (Hu et al., 2001). The contribution of obesity in T2DM development is about 90% (World health organization [WHO], 2011). The main factors involved in the development of T2DM are less insulin secretion and resistance of insulin in peripheral tissues like adipose tissues, muscles and liver (Butler et al., 2003; Kahn, 2003; Pratley & Weyer, 2001; Stumvoll et al., 2005). The most common Type of diabetes i.e., T2DM is marked by Hyperglycemia, resistance of insulin and deficiency of insulin (Maitra & Abbas, 2005). New studies evaluated that reduction in the function of α-cell also contributes in the development of T2DM (Fujioka, 2007). The worldwide prevalence of Diabetes mellitus was over 463 million in 2019, in which more than 90% of diabetes patients were diagnosed with T2DM. This prevalence is projected to be 578 million in 2030 and 700 million in 2045 (Saeedi et al., 2019).

1.2 Parkinson's Disease (PD)

Parkinson's disease (PD) is a developing and neurodegenerative disease that influences the regulation of body movements in a person by affecting coordination between brain and other parts of the body for the movements of the muscles (Rewar, 2015). PD usually arises about 60 year's age, but it may emerge earlier (Edinburg Regional Medical Center [ER], 2015). This disorder is developed by degeneration of neurons found in the "Substantia Nigra (SN)" of mid brain and the function of these nerve cells is production of dopamine (Parkinson's disease Information [PDI], 2015; Kumar et al., 2010). The exact cause of PD is still unknown, however both genetic and environmental factors are vital for its exposure (Shafique et al., 2011). The four major symptoms of PD are Tremor, bradykinesia (Slowness

of movement), rigidity (Muscles stiffness), and Postural Instability (Rewar, 2015). Other Symptoms include Dyskinesia, Dimentia (Imtiaz et al., 2016), Anosmia (absence of sense of smell), Anxiety, Constipation, Depression, Fatigue, festination of speech, Postural hypotension and Micrographia (Kalia & Lang, 2015; Chao et al., 2015). The worldwide prevalence of PD is about 6.5 million and it is predicted to be double in the upcoming 10-20 years (Imtiaz et al., 2016).

2. PROTEOMICS CORRELATION BETWEEN T2DM AND PD

Type 2 Diabetes mellitus and Parkinson's disease are very different in their etiology; however these two diseases are linked with each other as the Patients suffering from diabetes have 40% more risk for getting Parkinson's disease as compared to diabetes free individuals (Lima et al., 2014; Xu et al., 2011). Several cross-sectional and prospective studies have also revealed the linkages between Type 2 DM and PD through different surveys (Pressley et al., 2003). These studies raised number of questions about the interrelation between these two disorders. Few common molecular mechanisms are also involved among Type 2 DM and Parkinson's diseases including the protein misfolding, aggregation and amyloid synthesis, high secretion of methylglyoxal (MG) and insufficiency of dopamine (Aviles-Olmos et al., 2012; Fatima et al., 2014; Hipkiss, 2012; Tian et al., 2015).

The determination of the linkages between Type 2 Diabetes Mellitus (T2DM) and Parkinson's disease (PD) is very important; involving the common regulation of the proteins in T2DM and Parkinson's disease individuals possibly will reveal the association between these two diseases.

In this review article, the dysregulation of some important proteins has been revealed, having distinct association in the pathophysiological mechanisms of T2DM and PD such as autophagy dysregulation, mitochondrial damage (dysfunction), Endoplasmic reticulum (ER) stress (malfunction), inflammation and loss of central and peripheral synapse.

2.1 Amyloid Fibres

The aggregation of amyloid fibres from unfolded polypeptide plays a vital role in both Parkinson's disease and Type 2 diabetes mellitus, because amyloid structures are synthesized from amylin [islet amyloid polypeptide (IAPP)] in T2DM while amyloid like structures are synthesized from α-synuclein in Parkinson's disease. This linkage of IAPP and α-synuclein in the synthesis of amyloid make the association of these two disorders more complex (Surguchov, 2016).

2.2 Parkin and PINK 1:

Mitophagy is a quality control process in healthy neurons for removal of damaged or non-functional mitochondria to prevent cell death, neuronal cell death is caused by increased mitochondrial damage that leads to the pathogenesis of PD. Mitophagy or the capability of neurons to remove dysfunctional organelles (Mitochondria) is reduced by loss of Parkin or PINK1 (PTEN-induced putative kinase 1) proteins as a result these dysfunctional organelles are accumulated in the neurons and cause the early-onset PD (Pickrell & Youle, 2015). PINK1 identify dysfunction of mitochondria and then signals Parkin to ubiquitinate distinctively the non-functional mitochondria to initiate their removal by autophagy (Pickrell & Youle, 2015). This indicates that PINK1 and Parkin collectively have a mitochondrial quality control role and prevents Parkinsonism in human beings (Geisler et al., 2010). Auotphagy has very distinctive role in the homeostasis of islet and improvement of ß cell mass against a fat-enriched diet (Marrif & Al-Sunousi, 2016). Certain studies have concluded that the pathway of PINK1/PARKIN perform vital role in mitochondrial quality control in obese and T2DM. PINK1/PARKIN pathway mediated mitochondrial quality control mechanism is reduced by suppressing the transcription of PINK1 level in skeletal muscle tissues of obese and T2DM patients (Scheele et al., 2007). Additionally, pancreatic ß cells may be damaged by defective function of PARKIN causing decreased secretion of insulin (Hoshino et al., 2014).

2.3 Beclin:

Beclin is a protein associated with the nucleation phase of autophagy; its level was examined scarcely high in cerebral cortex and

hippocampus of type 2 diabetic mice. The level of ß-cell lymphoma 2 (a beclin repressor) was slightly down in the hippocampus of diabetic type 2 mice while the level of PI3K class III kinase (an activator for beclin-induced nucleation) has been examined high in the region of cerebral cortex and hippocampus of type 2 diabetic mice (Carvalho et al., 2015). Autophagy is a type of catabolism involved in the digestion of long-lived proteins and non-functional organelles in the cells of eukaryotes activated by various adverse conditions such as decreased level of nutrients, hypoxia and low energy supply, as a result these catabolic products especially amino acids are released into the cytoplasm for essential biosynthetic mechanisms (Lynch-Day et al., 2012). The primary function of autophagy is protection by regulating nutrient and energy homeostasis in a stressed condition, however it may also be involved in the pathogenesis of many neurodegenerative disorders, such as Alzheimer, Huntington's, and Parkinson's diseases because abnormal proteins and non-functional/damaged organelles are accumulated as a result of dysregulation of autophagy (Banerjee et al., 2010). Dysregulation of autophagy may be caused by abnormal Beclin-1 protein levels contributing in the pathogenesis of neurodegenerative disorders (Pickford et al., 2008; Nascimento-Ferreira et al., 2013; Lucin et al., 2013). For example, the level of Beclin-1 is low in many neurodegenerative diseases (Pickford et al., 2008) while high regulation of Beclin-1 improves the pathogenesis of neurodegenerative diseases in animal models (Nascimento-Ferreira et al., 2013). Autophagy is commonly activated via mTOR (mechanistic target of rapamycin) signaling pathway however additional or secondary signaling pathway for activation of autophagy is theVps34-Beclin-1complex to enhance cell survival. For instance, the aggregation of a-synuclein is reduced in case of high regulation of Beclin-1 to minimize cell death and maximize the activity of autophagy (Spencer et al. 2009).

2.4 ATG7:

The main role of ATG (autophagy related proteins) proteins is to control the formation of autophagosome, transportation to lysosomal portion and cargo gathering (Arroyo et al., 2014). Modification in these proteins can accommodate the clearance of impaired organelles and accumulated proteins. The level of ATG7 (Autophagy related 7)

was revealed extremely low in the cerebral cortex and hippocampus regions of type 2 Diabetic mice model, indicating that the phase of elongation for autophagosome synthesis has been agitated (Carvalho et al., 2015). ATG7 is an important autophagy protein needed for membrane transportation and degeneration of axonal terminals, and axonopathy linked with neurodegenration caused by deterioration of axonal autophagy (Komatsu et al., 2007). Vacuoles resembling autophagosome have also been revealed in the non-functional or degenerating axons linked with various kinds of chronic neurodegenerative disorders which include (Nixon et al., 2005; Cataldo et al., 1996), Parkinson's disease (PD) (Anglade et al., 1997), and animal models for neurodegenerative diseases (Yu et al., 2005; Lin al., 2003; Li et al., 2001). New research study suggests that minimal levels of autophagy preserve neurodegeneration because autophagy is important for the regulation of local homeostasis of axon terminals and prevent degeneration of axons (Komatsu et al., 2007). These findings indicate an association between locally modified autophagy and axonopathy, which is involved in neurodegeneration (Coleman, 2002).

2.5 LC3-II:

Autophagy is the main process for the breakdown and recycling of prolonged proteins and dysfunctional organelles inside cells (Klionsky, 2000; Lynch-Day et al., 2012). LC3s (MAP1-LC3s) are autophagosomal membranous structural proteins broadly used as biomarkers of autophagy (He et al., 2003; Bai, Inoue et al., 2012). LC3-II (microtubule-associated protein 1A/1B-light chain 3- II) is a type of LC3 which is the major constituent of the autophagosomal membrane found both on the inner and outer surface of the membrane. It has been obtained from a protein known as pro LC3 (30 KDa), which is cleaved by autophagin ATG4 to synthesize the form LC3-I activated by ATG7, and then shifted to ATG3 to develop into LC3- II bounded to the membrane (Ichimura et al., 2000). The LC3-II found in the outer region is discharged to the cytosol and the LC3-II found in the inner region is hydrolyzed by hydrolases after the synthesis of autophagosome (Kabeya et al., 2000). This latest form of LC3-II found on the membranes of autophagosome and autolysosome act as an appropriate marker of autophagy (Kabeya et al., 2000; Wu et

al., 2006). The level of LC3-II protein has been revealed slightly decrease in the cerebral cortex of type 2 Diabetic mice model (Carvalho et al., 2015).

2.6 Carnosinase (CNDP2):

Carnosinases are Xaa-His dipeptidases that have variety of roles in organisms. The isoforms of human carnosinase (CN1 and CN2) speed up the hydrolysis of the dipeptides carnosine (β-alanyl-L-histidine) and homocarnosine (γ-aminobutyryl-L-histidine) under suitable conditions. The deregulation of expression and activity of carnosinase leads to certain physiological defects and disorders like diabetes mellitus, ischemia and neurological disorders (Bellia et al., 2014). Carnosinase, CNDP2 (Carnosine Dipeptidase 2) has shown increase activity in the SN of PD patients through several proteomic studies therefore it is suggested that carnosine (CAR) make effort for protection against PD outbreak by reacting with MG and by interfering with glycolysis (Hipkiss, 2012). Carnosinase influences the metabolism of glucose and prevents diabetic deterioration (Lee et al., 2005; Sauerhofer et al., 2007). It is suggested that the existence of CAR, homocarnosine and anserine in central nervous system and their aging alterations (Hipkiss, 2005; Huang et al., 2005) have a therapeutic characteristic in neurodegenerative diseases (Hipkiss, 2007). Carnosine is neuro-protective because it has the potential to neutralize both oxidative (La-Mendola et al, 2002) and nitrosative stress (Fontana, Pinnen, Lucente & Pecci, 2002) in pathological conditions (Dukic-Stefanovic et al., 2001; Pubill et al., 2002) , like ischemia (Tang et al., 2007). CNDP1 (Carnosine Dipeptidase 1) has low activity levels in neurological disorders including Parkinson's disease (Butterworth et al., 1996). On the other side, CNDP2 is highly expressed in the SN of PD (Licker et al., 2012). Therefore carnosine has a neuroprotective role by lowering neurotoxicity through its antioxidant potential (Trombley et al., 2000). The linkage between normal kidney function and tissue carnosinase activities has been revealed suggesting that CAR may have protective role in human diabetic kidney disease (Janssen et al., 2005). It is also suggested that increased diabetic nephropathy may be due to MG reveals that high level of carnosine may have role in the suppression of MG-mediated pathology. Despite, the observations that pathology is elevated when

the activity of carnosinase is high in both kidney and SN is consistent with the proposal that carnosine may employ some protective activity towards MG-mediated molecular modification (Hipkiss, 2012).The physiology for the protective response of (CTG) 5 homozygosity recommend that decreased activity of carnosinase stimulates high level of circulating carnosine that provide protection in contrast to hyperglycemia- induced cytotoxic metabolites emerging from oxidative stress and glycation (Freedman et al., 2007). Human serum carnosinase has been suggested as a novel biomarker in (cerebral spinal fluid) CSF (Hu et al., 2007; Perrin et al., 2011).

2.7 Synaptophysin:

Synaptophysin or a major synaptic vesicle protein p38 is expressed in nerve cells and has been marked as a specialized presynaptic marker for neurons (Calhoun et al., 1996). The cortex of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- induced monkey model of Parkinson's disease (PD) (Raju et al., 2008), dementia with Lewy bodies and other neurodegenerative disorders are characterized with loss of synaptophysin or low level of synaptophysin (Mukaetova-Ladinska et al., 2013) Dementia is a prevalent problem and trait of many neurodegenerative disorders such as Parkinson's disease (Bossy-Wetzel et al., 2004). While a research study has revealed slight decrease of synaptophysin in the hippocampus of T2DM mice (Carvalho et al., 2015).

2.8 SNAP-25:

Synaptosomal-associated protein of 25 KDa (SNAP-25) is known to be a presynaptic protein necessary for releasing of neurotransmitter (Corradini et al., 2009). The Ser187 of SNAP-25 is phosphorylated by protein kinase C (PKC) to increase the generation of neurotransmitter by recruiting secretory vesicles adjacent to the plasma membrane however a mutant mouse, substituting Ser187 of SNAP-25 with Alanine has been characterized by decreased dopamine release (Kataoka et al., 2011). PD is characterized by continuous degeneration of dopaminergic neurons in the SN pars compacta (Videira & Castro-Caldas, 2018). The level of SNAP-25 was shown low in the cerebral cortex and hippocampus of type 2 diabetic mice model (Carvalho et al., 2015).

2.9 Sorcin:

Sorcin is a calcium sensor protein involved in regulating ER Ca2+ by inhibiting ryanodine receptor activity and playing a role in terminating Ca2+ induced Ca2+ release (Marmugi et al., 2016). The pathogenesis of type 2 diabetes is characterized by dysfunction of ß-cells of pancreas, Islets of Langerhans enlarges the mass of ß-cell and increases the production of insulin in the promotion of obesity and resistance of insulin (Prentki, 2006). Chronic hyperglycemia increases the necessity of biosynthesis of insulin and also rise the flowing free fatty acids and cytokines lower endoplasmic reticulum (ER) calcium (Ca2+) stores (Cunha et al., 2008; Ramadan et al., 2011), causing ER stress and apoptosis (programmed cell death) in prolonged cases (Arruda & Hotamisligil, 2015). Sorcin exhibits a process to dysregulate the function of b-cell in metabolic stress by linking lipotoxicity of b-cell to endoplasmic reticulum calcium and stress of ER Thus, it is revealed that sorcin is expressed lower in pancreatic ß-cells under lipotoxic stress, whereas overexpression of sorcin is enough to prevent failure of ß-cell and glucose intolerance. Therefore Sorcin may present a target for interference in type 2 Diabetes mellitus (Marmugi et al., 2016). Sorcin has shown to be differentially upregulated in PD (Werner, Heyny-von Haussen, Mall & Wolf, 2008).

2.10 GLP-1 analogues:

The incidence of type 2 diabetes increases the occurrences of Parkinson's disease in type 2 diabetes affected patients. The T2DM and PD share some common pathological mechanisms including dysregulation of insulin. Therefore, the homeostasis of gut-brain axis for healthy central nervous system and peripheral nervous system is an important process in this case (Kim et al., 2017). The type of endogen incretin hormones called Glucagon-like peptide-1 (GLP-1), maintains the releasing of insulin. The outcomes of GLP-1 is dealt by the G-protein and GLP-1 receptor mediate the consequences of GLP-1 which rise the cyclic AMP within cells then protein kinase-A and phosphoinositide 3-kinase are activated resulting phosphorylation of certain subsequent signaling pathways. The pancreas and periphery mostly contain the above mentioned receptors but they are expressed in the frontal cortex, hypothalamus, thalamus, hippocampus, cerebellum and substantia nigra of central nervous system (Athauda

& Foltynie, 2018). These receptors are involved in the generation of nervous tissues, reduction of inflammation, synaptic plasticity, suppressing apoptotic mechanism and boosting the function of mitochondria in the brain (Kim et al., 2017).

Exenatide is synthetically derived from exendin (EX-4). EX-4 is an activator of the GLP-1 hormone regulating insulin and glucose concentration (Aviles-Olmos et al., 2013). EX-4 is applicable in T2DM presently however the therapeutic capability of EX-4 in PD affected persons must be analyzed instantly (Harkavyi et al., 2008). Limiting microglial activation and expression of matrix metalloproteinase-3 by EX-4 has been revealed to influence neural development, support neuronal differentiation, and conserve degeneration of nerve cells through neurotrophic mechanism (Harkavyi et al., 2008; Kim et al., 2009 ; Li et al., 2009; Perry et al., 2002; Perry et al., 2002). Early stage treatment of PD rat model by EX-4, accommodated betterment in behavior and dopamine repairing (Rampersaud et al., 2012). Liraglutide and lixisenatide are the new derivatives of GLP-1 that played a neuroprotective role in PD mouse model by inhibiting apoptosis, by promoting motor impairment and by saving the concentration of tyrosine hydroxylase in the regions of Substantia nigra and basal ganglia (Liu et al., 2015). Another study has concluded that Some of GLP-1 agonists (sitagliptin, a dipeptidyl peptidase-4 inhibitor deactivating GLP-1, and liraglutide, GLP-1 mimetic) enhanced motor functions, prevent nigral degeneration and increase striatal dopamine in rotenone rat model of PD (Badawi et al., 2017). Saxagliptin which is a dipeptidyl peptidase-4 inhibitor has significantly improved motor functions and prevent immunoreaction of tyrosine hydroxylase in Substantia nigra by inhibiting oxidation, inflammation, apoptosis and activating mechanisms of neuroprotection and neurorestoration (Nassar et al., 2015).

2.11 AMPK:

Neurodegeneration in PD may be improved by triggering adenosine monophosphate-activated protein kinase (AMPK) (Choi et al., 2010). Metformin is a class of oral diabetes medication generally used in T2DM and protect against inflammation by activating AMPK (Hang et al., 2015; Ismaiel et al., 2016). Many studies have adverse results showing that neuronal cell loss has been avoided in MPP+/MPTP

animal models of PD by the activation of AMPK (Choi et al., 2010) The result of a research study revealed that AMPK deals decline of dopamine releasing nerve cells in PD mice models and the neurodegeneration in those mice is increased by metformin (Kim et al., 2013). A cohort study among the Taiwanese population surprisingly revealed that the risk of PD was double in the patients suffering from T2DM but this risk can be lowered by using metformin as a conjoint therapy, expressing that metformin is functional to activate AMPK (Wahlqvist et al., 2012). Recently a study has affirmed that prolong application of metformin for type 2 diabetic patients can develop disorders of neurodegeneration like dementia and Parkinson's disease (Kuan et al., 2017).

2.12 Aldehyde dehydrogenase A1 (ADH1A-1):

Aldehyde dehydrogenase A-1 (ALDH1A-1) is a multifaceted enzyme with dehydrogenase, esterase, and anti-oxidant activities and regulates retinoic acid (RA) signaling, which is crucial for the homeostasis of normal brain (Nikhil et al., 2018). ADH1A-1 was differentially overexpressed in the Substantia nigra of PD patient in contrast to controls, which is an enzyme associated with the metabolism of aldehyde (Werner et al., 2008) and dopamine metabolites (Grünblatt & Riederer, 2014). The level of ALDH1A-1 was low in PD brains, and ALDH1A-1 and ALDH2 double knockout mice revealed high HNE (4-hydroxy-2-nonenal) and 3,4-dihydroxyphenylacetaldehyde and remarkable dopaminergic neurodegeneration (Grünblatt & Riederer, 2014). Prolong oxidative stress caused by Cdk5 (Cyclin Dependent Kinase-5) inhibits ALDH1A-1 activity to generate neurotoxicity and overexpression of ALDH1A-1 play vital role in neuroprotection in terms of neurodegenerative disorders (Nikhil et al., 2018). Recently a research study has reported the discovery of an isoform of aldehyde dehydrogenase-1 isoform A3 (ALDH1A-3) as a biomarker of nonfunctional b cells in diabetic mice (Kim-Muller et al., 2016). ALDH1A-3 was markedly absent from normal b cells (Kutlu et al., 2009). A recent study has concluded that ALDH1A-3 is also raised in the pancreatic islets of type 2 diabetic patients (Cinti et al., 2016).

3. DISCUSSION

A link between type 2 diabetes mellitus (T2DM) and Parkinson's disease (PD) has been suggested for decades. Number of common risk factors has been suggested for T2DM and PD, including oxidative stress, autophagy dysregulation, mitochondrial damage (dysfunction), Endoplasmic reticulum stress (malfunction), inflammation and loss of central and peripheral synapse. T2DM and PD both are considered protein conformational diseases. Protein misfolding disorders (PMDs) are diseases in which misfolding, aggregation and accumulation of proteins occur in the disease-specific damaging tissues. Both Parkinson's disease (PD) and type 2 diabetes mellitus (T2DM) are the examples of PMDs (Soto, 2003).The first line of evidence that linked T2DM and PD is protein misfolding and aggregation of amyloid fibres. Amyloid fibres are synthesized from amylin [islet amyloid polypeptide (IAPP)] in T2DM while amyloid like structures are synthesized from α-synuclein in PD (Surguchov, 2016).

Autophagy is a molecular mechanism needed for regulation of cellular physiology and promoting cell survival however defects in autophagy lead to the pathogenesis of several disorders, including Diabetes Mellitus and neurodegeneration. Autophagy eliminates dysfunctional organelles, lipids and miss-folded proteins in T2DM. Additionally, autophagy perform vital role in dysfunction of pancreatic ß-cell and resistance to insulin (Yang et al., 2017). Oxidative stress, mitochondrial dysfunction, and protein aggregation play an important role in the pathogenesis of PD; these factors are highly associated to autophagy. The brains of PD patients and animal models of PD have been characterized by dysregulation of autophagy in a recent study, suggesting the developing role of autophagy in PD (Lynch-Day et al., 2012). Mitophagy is a quality control process in healthy neurons for removal of damaged or non-functional mitochondria to prevent cell death (Pickrell & Youle, 2015).

In this review article, it is determined that autophagy induction can be analyzed by different proteins, such as Parkin and PINK 1, Beclin, AMPK, ATG7 and LC3-II in T2DM and PD. Certain studies have concluded that the pathway of PINK1/PARKIN perform vital role in mitochondrial quality control in T2DM and PD (Geisler et al., 2010; Scheele et al., 2007). Dysregulation of autophagy is due to reduction of PINK1/PARKIN level which leads to the pathogenesis of

T2DM and PD. Beclin is a protein associated with the nucleation phase of autophagy, the level of Beclin and Beclin-1 was slightly high in the T2DM and PD respectively suggesting that it minimizes cell death and maximizes the activity of autophagy (Spencer et al. 2009; Carvalho et al., 2015). The level of ATG7 was revealed extremely low in type 2 diabetic mice model, indicating that the elongation phase of the autophagosome synthesis has been agitated (Carvalho et al., 2015). On the other hand, ATG7 is an important autophagy protein needed for degeneration of axonal terminals, and axonopathy linked with neurodegeneration caused by deterioration of axonal autophagy (Komatsu et al., 2007). It has been concluded by a recent study that minimal level of autophagy preserve neurodegeneration (Komatsu et al., 2007). LC3-II is a type of LC3 which is the major constituent of the autophagosomal membrane found both on the inner and outer surface of the membrane. The LC3-II found on the membranes acts as a marker for autophagy (Kabeya et al., 2000; Wu et al., 2006). The level of LC3-II protein has been revealed slightly decreased in the cerebral cortex of type 2 diabetic mice model (Carvalho et al., 2015) indicating that this protein plays vital role in the pathogenesis of T2DM. Autophagy is also important for the pathogenesis of PD however the role of LC3-II in PD related autophagy has not been observed.

Sorcin is another protein dysregulating the function of pancreatic ß-cell in metabolic stress by linking lipotoxicity of ß-cell to endoplasmic reticulum calcium and stress of ER. It has been revealed that the overexpression of sorcin is enough to prevent failure of ß-cells and glucose intolerance. Thus, it may present a target for interference in type 2 diabetes mellitus (Marmugi et al., 2016). Sorcin has shown to be differentially overexpressed in PD (Werner et al., 2008) however the role of sorcin in the development of PD has not been revealed by a study. The above findings suggest that sorcin perform an important role in the pathogenesis of T2DM and PD.

The overexpression of ALDH1A-1 performs vital role in neuroprotection in terms of neurodegeneration (Nikhil et al., 2018). The level of this enzyme has been observed decrease in the SN of PD brain (Werner et al., 2008) indicating its importance in the pathogenesis of PD. The role of ALDH1A-1 in T2DM has not been observed by a study however an isoform of ALDH1 isoform A3

(ALDH1A3) has been discovered as a biomarker of nonfunctional b cells in diabetic mice (Kim-Muller et al., 2016). A recent study has concluded that ALDH1A3 is also raised in the pancreatic islets of type 2 diabetic patients (Cinti et al., 2016).

Synaptophysin and SNAP-25 are presynaptic proteins/markers in neurons for releasing of neurotransmitters. The level of both proteins has been revealed decrease in T2DM and PD (Mukaetova-Ladinska et al., 2013; Carvalho, 2015). Mutation of SNAP-25 protein in mouse model of PD leads to decrease dopamine release (Kataoka et al., 2011). The role of these two proteins in the development of T2DM and PD need further research studies.

Neurodegeneration in PD and inflammation in T2DM may be improved by activating AMPK through the administration of Metformin (Choi et al., 2010; Hang et al., 2015; Ismaiel et al., 2016). Activation of AMPK by Metformin in the treatment of T2DM and PD shows links between these two diseases.

Pancreas contains receptors for GLP1 analogues but they are expressed in different regions of brain (Athauda & Foltynie, 2018). These receptors are also involved in the growth of nervous tissues, prevention of inflammation, synaptic plasticity, suppressing apoptotic process and boosting the function of mitochondria in brain (Kim et al., 2017). GLP-1 may also link the pathogenesis of T2DM and PD. An agonist of GLP-1 known as EX-4 is applicable in the treatment of type 2 diabetic patients however the therapeutic capability of EX-4 in PD affected persons must be trialed instantly (Harkavyi et al., 2008).

The activity of Carnosinase, CNDP2 has been increased in SN of PD suggesting that carnosine make effort for protection against PD (Hipkiss, 2012) and it influences the metabolism of glucose and prevents diabetic deterioration (Lee et al., 2005; Sauerhofer et al., 2007).

4. CONCLUSION

Different literature analyses in this study find out some common proteins involvement in the pathogenesis of both diseases (T2DM and PD). These proteins include amyloid fibres, Parkin & PINK1, Beclin, ATG7, LC3-II, Carnosinase (CNDP2), Synaptophysin, SNAP-25, Sorcin, GLP-1 analogues, AMPK and ADH1A1. Dysregulation of these

proteins causes oxidative stress, autophagy dysregulation, mitochondrial damage (dysfunction), Endoplasmic reticulum stress (malfunction), inflammation and loss of central and peripheral synapses in T2DM and PD.

Although the above findings suggest that type 2 diabetes mellitus and Parkinson's disease are associated through various pathways but there is no conclusive evidence to prove that T2DM is a risk factor for the development of PD. Further prospective, pathological and proteomics studies are required to clarify the correlation of T2DM with PD.

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Abbreviations used:

T2DM, Type 2 Diabetes Mellitus; PD, Parkinson's Disease; SN, Substantia Nigra; MG, Methylglyoxal; CAR, Carnosine; CNDP1, Carnosine Dipeptidase 1; CNDP2, Carnosine Dipeptidase 2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ; SNAP-25, Synaptosomal-associated protein of 25 KDa; GLP-1, Glucagon-like peptide 1; IAPP, islet amyloid polypeptide; AMPK, Adenosine monophosphate-activated protein kinase; LC3-II, Microtubule-associated protein 1A/1B-light chain 3- II; ADH1A1, Aldehyde dehydrogenase 1A1; ALDH2, Aldehyde Dehydrogenase 2; ALDH1A3, Aldehyde Dehydrogenase 1 Family Member A3; ATG Proteins, Autophagy related proteins; ATG7, Autophagy related 7; ER, Endoplasmic Reticulum; PINK1, PTEN-induced putative kinase 1.

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