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Diabetes-Driven Oxidative Stress: A Cascade From Inflammation To Neuroinflammation And Emerging Therapeutic Strategies

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ABSTRACT:-

It is becoming more widely acknowledged that chronic diabetes mellitus (DM) increases the incidence of neurodegenerative illnesses, including Parkinson's disease (PD). Oxidative stress as well as neuroinflammation stand highlighted as important, interconnected drivers for dopaminergic neurodegeneration among the major mechanisms connecting these two disorders. Diabetes-related chronic hyper glycemia results in a compromised antioxidant defense system, increased generation in reactive oxygen molecules (ROS) and compromised mitochondrial activity. Due to their great susceptibility to oxidative insults, dopamine-producing neurons of the substantia nigra are especially affected by the prolonged oxidative stress caused by these alterations.

Furthermore, neuroprotective pathways may be disrupted by poor insulin transmission in the brain, making neurons even more susceptible to oxidative & inflammatory assaults. Oxidative stress & neuroinflammation are key and perhaps changeable pathways in diabetes-induced neurodegeneration, even though other elements like mitochondrial malfunction and protein aggregation (like α-synuclein) also contribute to Parkinson's disease pathogenesis.

α-synuclein aggregation & dopaminergic cell death are two classic PD diseases that are caused by the synergistic combination of oxidative stress and neuroinflammation, which upsets neuronal homeostasis. These results highlight how crucial it is to target oxidative & inflammatory pathways in diabetic populations help prevent or delay the emergence of Parkinson's disease. One promising approach to risk reduction and therapeutic intervention is to address these pathways.

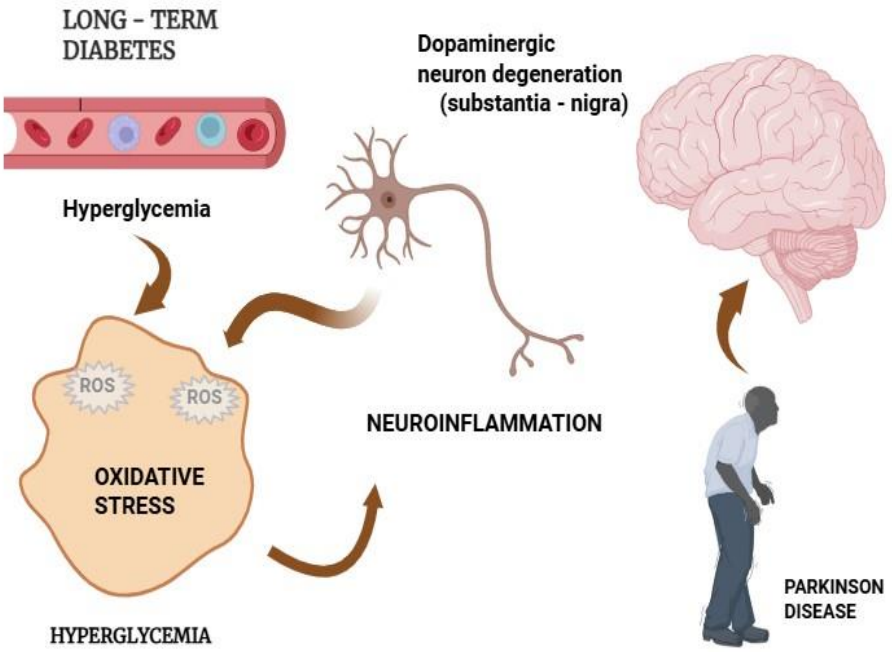

Fig 1:-Diagrammatic representation of how oxidative stress and neuroinflammation brought on by hyperglycemia contribute to the development of Parkinson's disease

KEY WORDS: Diabetes, Oxidative stress Neuroinflammation, Parkinson

1. INTRODUCTION:-

Type 2 diabetes is a chronic metabolic illness marked by a reduction in β-cell function and population and activity in addition to an extended tolerance to insulin. These factors inhibit insulin from being released, leading to hyperglycemia[1].A biological phenomenon known as insulin resistance occurs when peripheral tissue cells are unable to absorb glucose from the blood and do not react to insulin as well. Hyperglycemia, hyperinsulinemia, and hyperlipidemia are caused by insulin resistance and contribute to the pathophysiology of Diabetes type 2[3].It affects more than 400 million people, according to WHO[8].Parkinson's disease (PD), a degenerative neurological condition with extensive clinical manifestations affecting both central and peripheral tissues, is typified by the decline of nigrostriatal dopamine-producing neurons[2].Epidemiological studies demonstrate that diabetes is an associated an increased chance of Parkinson's disease (PD), and the onset of diabetes seems to exacerbate symptoms in PD patients. Numerous research have attempted to clarify how T2D influences the etiology and development of Parkinson's disease.[3].PD and type 2 diabetes are prevalent conditions that have a detrimental impact on patients' quality of life. It is essential for us to look into these disorders' relationships and interactions, in addition to studying them as separate entities [1].Polyuria (frequent urine), polydipsia (increased thirst), and polyphagia (increased appetite) are the traditional signs of diabetes[4]. Although the precise pathophysiological processes causing neurodegeneration in the PD brain are yet unknown, there is strong evidence that the pathophysiology of PD is mostly influenced by autophagy system malfunction, inflammation, oxidative stress, and mitochondrial dysfunction[5]. The second most prevalent condition is Parkinson's disease (PD), neurodegenerative disease that affects roughly 1% of adults over 65 and 4-5% of those over 85 years[6].Furthermore, since PD is becoming more common in an aging society, it is estimated that the proportion of people affected by the disease will double over the three decades that follow[7].PD and DM share a number of commonalities. The degeneration of certain cells—in DM, the beta-pancreatic cells and the pigmented dopaminergic cells in PD—causes the clinical signs of both disorders. When these cells are lost, dopamine levels in PD and insulin concentrations in DM decline [8].

2. PATHOPHYSIOLOGY:-

A complex metabolic disorder, diabetes mellitus (DM), is marked by the physiologically aberrant state of hyperglycemia characterized by constant increased levels of blood glucose. Dysfunctions in the breakdown of carbohydrates, fats, and proteins are chronic and various signs of hyperglycemia, it can be caused by abnormalities in either insulin secretion, insulin action, or both.[9]

Autoimmune-mediated β-cell destruction is a hallmark of type 1 diabetes (T1DM), an immune system disease marked by a number of immune markers, including autoantibodies, such as glutamic acid decarboxylase antigen-specific antibodies (GADAs) like GAD65, islet cell antigen-specific antibodies (ICAs) to β-cell cytoplasmic proteins, like cell autoantibodies to islet cell antigen [10]. These antigens are taken up by dendritic cells (DCs) and then distributed to T cells. An auto-immune reaction can only happen if autoreactive T cells have avoided thymic negative selection. Autoreactive T cells stimulate B cells and autoreactive cytotoxic T when they are activated by DC. Finally, DCs, natural killer (NK) cells, T, B, and macrophages have to function collectively to implement the beta-cell death effector mechanism [11]. T2DM is characterized by two main pathogenic features: IR (caused by oxidative stress) in targeted organs and impairments in the production of insulin or action as a result of pancreatic β-cell malfunction [12].The pancreatic islets always produce and store insulin in vacuoles during regular physiological circumstances, independent of the blood's glycaemic level. The release of insulin is further triggered by the growing blood glucose levels.Insulin then controls the absorption of glucose in the skeletal muscles and adipose tissues [12].

2.1. FREE RADICAL - these are chemical entities that are typically very reactive and have an unpaired electron. They are pieces of molecules. Cells continuously create them, either purposefully during processes like phagocytosis or as unintentional byproducts of metabolism [47].

ROLE OF FREE RADICAL:-

Free radicals, as well as and other non-radical reactive derivatives, cited to as oxidants, are together referred to as reactive nitrogen compounds (RNS) and reactive oxygen molecules (ROS). Their electrons have the ability to react with a variety of organic substrates, including proteins, lipids, and DNA [9].They have positive effects at lower doses and participate in various physiological processes, including immunological function, cellular signaling pathways, mitogenic responses, and redox control [60] Reactive nitrogen species (RNS) consist of nitric oxide (NO), that is not very reactive, and its byproduct, peroxynitrite, a potent oxidant, ROS comprise molecules such as the hydroxyl radical (OH), which has a very high reactivity, and superoxide and hydrogen peroxide (H2O2), and that are less reactive.[16]Under normal reduced conditions, hydrogen peroxide and superoxide anion are formed from only 1% to 2% of total oxygen consumption. Around ten percent of all the respiratory oxygen that is taken in, however, may be wasted as free radicals when hyperglycemia is present [18] Lipid peroxidation, the oxidation of polyunsaturated fatty acids in physiological systems, can be attacked by free radicals. People with type 2 diabetes, metabolic syndrome, and obesity have higher levels of lipid peroxidation byproducts like conjugated dienes as well as malondialdehyde (MDA) [61]. One of oxidative stress's primary causes that results in over type 2 diabetes [14]. When fatty acid beta oxidation is blocked and ROS production is subsequently increased, mitochondrial abnormalities change the equilibrium between prooxidant and antioxidant processes, increasing the amount of non metabolized fatty acids in the cytosol [15].

2.1.1. ACTIVATION OF POLYOL PATHWAY:-

Under normal circumstances, cellular glucose is primarily Hexokinase-phosphorylated to create glucose-6-phosphate in order to move through the glycolytic pathway. The polyol pathway only receives small quantities of non-phosphorylated glucose (~3%) [62] When there is persistent hyperglycemia, the Polyol pathway is activated. This pathway is thought to metabolize about 30% of the body's glucose, resulting in a NADH/NAD+ imbalance of redox that fuels diabetes’s oxidative stress [18]. In addition to sorbitol dehydrogenase, aldose reductase (AR), catalyze two processes in this route. Sorbitol dehydrogenase uses NAD+ to convert sorbitol to fructose, resulting in the creation of NADH, whereas AR lowers sorbitol from glucose at the price of NADPH. [48] Since the polyol pathway changes NAD+ into NADH, it disrupts the oxidation reduction equilibrium among NAD+ and NADH , which is crucial

for counterbalancing redox in diabetics. In the electron transport chain's initial stage, it promotes the creation of ROS by causing an excess of NADH.[49]

The polyol pathway may cause oxidative stress through two different methods are the NADPH co - factor, where it is also necessary to regenerate GSH by glutathione reductase, is depleted by AR's activity and its co- factor NAD+ is changed into NADH during the of sorbitol to fructose's oxidation by SDH, and since NADH is the substrate for NADH oxidase to produce ROS, oxidative stress results. [50]

2.1.2. ENDOPLASMIC RETICULUM STRESS:-

Protein production and transportation protein folding, lipid biosynthesis, calcium homeostasis maintenance, and involvement in other essential cellular processes are among the roles played by the endoplasmic reticulum (ER) [63]. This disorder involves endoplasmic reticulum malfunction brought on by chemical or physical causes that cause the ER to respond with homeostatic compensatory responses [51] .ER stress, which is caused by changes in the oxidizing environment of the ER lumen, might result in the accumulation of misfolded polypeptides and the creation of illegitimate disulfide bonds [58].The ER stress response, also known as the UPR, is a coping mechanism that is triggered when ER stress is activated. Its function is to restore balance in the ER and stimulate the production of genes which prevent the accumulation of misfolded proteins [67]. The unfolding protein response (UPR) is an adaptive signaling pathway that the cells start in response to ER stress. [67] Unfolded Protein Responses (UPR) sensors proteins are particular ER membrane-bound proteins that are thought to be responsible for ER function impairment. [64]. The UPR thus maladaptive "overshoots" if the cell still experiences ER stress at rates that cannot be corrected, leading to apoptosis, arrest of the cell cycle, the dedifferentiation, aging, and sterile inflammation.[65] . In addition to physiological fluctuations in glucose, other circumstances including metabolic dysregulation linked to obesity, which includes extra foods and inflammatory cytokines, can also make the pancreatic beta cells vulnerable to ER stress [52].By reducing the number of insulin receptor cells on the cell surface, ER stress prevents insulin signaling.By obstructing the movement of freshly produced insulin pro receptors from the ER toward the plasma membrane, it prevents the proteolytic maturation of insulin pro receptors.[53]Glutathione (GSH), endoplasmic reticulum (ER) oxidoreductin 1 (ERO1), & native proteins disulfide isomerases (PDI) work together as a chaperone-like aided mechanism to prevent and repair abnormal disulfide bonds. This oxidative folding mechanism contributes to redox imbalance by depleting the GSH pool and producing a lot of ROS. [66]

2.1.3. OXIDATIVE STRESS'S IMPACT ON DIABETES MELLITUS:-

Oxidative stress is the result of free radicals exceeding the body's propensity to control free radicals [59] .The primary source of ROS generation and an organelle that is targeted by oxidative stress is the mitochondria [15]. The expression "redox system imbalance" refers to the oxidative stress caused by the degree of a disparity between antioxidants and oxidants [13]. Diabetes are recognized to be linked to oxidative stress and persistent inflammation .Cellular dysfunction can result from high ROS levels because they alter the composition and function of cellular proteins and lipids [19].These procedures use molecular oxygen and generate ROS, such as H2O2 and superoxide anion (O2-). Superoxide is rapidly converted to H2O2 by superoxide dismutase (SOD), and H2O2 is subsequently converted to H2O by catalase [76].

2.2. A DECLINE IN ANTIOXIDANTS DUE TO AN INCREASE IN OXIDATIVE STRESS:-

Antioxidant is "any substance that, when present at low concentrations compared with that of an oxidizable substrate, significantly delays or inhibits oxidation of that substrate".There are two different ways that antioxidants work[20] .The main method is a chain-breaking procedure in which an antioxidant neutralizes a free radical by donating an electron, stopping more oxidative damage. The secondary process, on the other hand, involves the removal of catalysts known as reactive species of nitrogen initiators, that start oxidative chain reactions[21].In general circumstances, the body can use antioxidants on three separate levels: (a) prevention, which involves limiting the production of reactive species, like desferrioxamine; (b) interception using both catalytic and non-catalytic compounds, like alpha tocopherol and ascorbic acid, to scavenge reactive species and (c) mending damaged target molecules, such as glutathione[22].The two most commonly utilized criteria, the antioxidant mode of

activity (primary and secondary antioxidants) as well as catalysis considerations (enzymatic and non-enzymatic antioxidants), were taken into consideration in the majority of the research that classified antioxidants[23].Nowadays, a variety of antioxidants, including endogenous, dietary, synthetic, and natural antioxidants, are present in food[20].

2.2.1. ANTIOXIDANTS:-

The imbalance among oxidants and antioxidants was the indication of oxidative stress [25].While hyperglycaemia during diabetes causes free radicals, it also negatively impacts the body's natural antioxidant defenses in numerous ways [26].Free radicals perhaps countered byby antioxidants such as superoxide dismutase (SOD) and ascorbic acid (Vitamin C) [27].An antioxidant undergoes oxidation when it eliminates a free radical. As a result, the body has to continuously replenish its antioxidant reserves. Therefore, an antioxidant may become ineffective against free radicals in some systems while being efficient against them in others [28].

2.2.2. DEPLETION OF ENDOGENOUS ANTIOXIDANTS:-

Endogenous antioxidants are either enzymatic or non-enzymatic byproducts of the body's metabolism[29].Although they are crucial in reducing ROS-mediated damage to biological macromolecules, they cannot be completely successful due to the high reactivity of some of the chemicals produced when ROS interact with macromolecules[30]. Particularly, catalase catalyses the breakdown of hydrogen peroxide, a class of antioxidant enzyme glutathione peroxidase contain selenium and are crucial for hydro peroxide reduction [24].GSH reduces H2O2 into water and oxygen by donating its electron to it [31]. An indication of oxidative stress is an excessive rise in reactive oxygenated species which is supported by either a weak antioxidant defense or a failure of the cells' buffering system to keep up the redox equilibrium. This causes a variety of changes in biomolecules, which in turn define the disease condition [32].

2.3. NEUROINFLAMMATION:-

The word "neuroinflammation" refers to inflammation of the CNS (central nervous system) in specific as well as inflammation of neural tissue in general[33].When different immune cells (such as microglia, astrocytes endothelial cells) release inflammatory mediators in response to a range of hazardous condition this is known as neuroinflammation[34].Originally a protective response, neuroinflammation has since been shown to be a major factor in the development of many neurological conditions, particularly degenerative diseases, when it persists over an extended period of time[35].

Reactive species secreted by inflammatory cells result in oxidative stress Certain ROS and RNS have the ability to further stimulate intracellular signalling cascades [36]. The overproduction of ROS by mitochondria and leukocyte and endothelial cell NADPH oxidase, which is not offset by antioxidant systems, can cause major tissue and cellular damage as well as chronic inflammation, which is the root cause of many neurodegenerative diseases[37].When ROS levels are too high, they can seriously harm many molecules, including lipid peroxidation, protein oxidation, and DNA damage[38].The overproduction of ROS, which can harm cellular constituents including lipids, proteins, or DNA, is referred to as oxidative stress[39].Additionally, too much ROS triggers the pro-inflammatory transcription factor activation like Activator Protein-1 and Nuclear factor kappa-light-chain-enhancer of activated B cells which in turn enhances the production of cytokines, chemokines, and adhesion molecules that promote inflammation[40].As mediators of inflammatory signaling, cytokines attach to their specific receptors and either trigger the generation of reactive oxygen species (ROS) or trigger the activation of transcription factors or kinases, which in turn trigger the induction of additional inflammatory signals[41].It is evident that certain cytokines affect brain endothelial cells, which may cause the BBB's restrictive features to be disrupted or altered[42,43].One prevalent contributing factor to the onset and progression of CNS illnesses, including neurodegenerative diseases like Alzheimer's disease, Parkinson disease and stroke, is inflammation in the peripheral area in the form of infection[44].

3. PATHWAY OF PARKINSONISM THROUGH OXIDATIVE STRESS AND NEUROINFLAMMATION:-

One of the most common disorders disrupting the CNS (central nervous system) is Parkinson's disease (PD), a progressive neurodegenerative illness [45]. It is distinguished by the predominant degradation of nigrostriatal neurons that produce dopamine, resulting in Parkinson's disease patients to experience movement symptoms[46].The typical hallmark of Parkinson's disease is a significant drop in dopamine (DA) levels in the nigro-striato-pallidal system[54,55]. The increase in blood glucose levels is without a doubt the main contributor to oxidative stress. Actually, once glucose enters cells, it is oxidized by the glycolytic pathway or the pathway involving pentose phosphate, which produces biosynthetic molecules and NADPH[56].0.2–2% of the electrons present in the ETC fail to follow the typical transfer order under healthy conditions; instead, they flow out of the ETC directly and combine with oxygen to form hydrogen peroxide or superoxide[57].Overproduction of the superoxide anions radical (O2radical dot) occurs in hyperglycemic situations (high blood glucose), which cause damages nuclear DNA and other proteins[68].

The enzyme called aldose reductase (AR) transforms glucose into sorbitol; this reaction requires the cofactor NADPH to provide an electron, which transforms it into NADP+[71] in the first step of the polyol pathway, while sorbitol dehydrogenase oxidizes sorbitol to fructose in the second step[69].It has been proposed that NADPH levels could be considerably reduced as glucose transit via the polyol pathway burns NADPH[70].Intracellular oxidative stress may be caused or made worse by NADPH since it is a cofactor needed to produce decreased glutathione, which is an antioxidant mechanism and a significant consumer of the reactive oxygen species (ROS)[72].

AGEs build up as a result of elevated sugar and reactive dicarbonyl molecules, including triosephosphates, glyoxal, fructose, deoxyglucose, and methylglyoxal (MGO)[73].Early in the Maillard process, a reducing sugar, like glucose, forms the Schiff base by non-enzymatically combining with the protein's free amino group. After that, the Schiff base undergoes a rearrangement process that produces the Amadori product, a more stable molecule [74].When AGEs attach to Toll-like, scavenger, G-protein-coupled, and pattern recognition receptors, they can alter cellular processes. The most significant among them is Advancement glycation end product receptor (RAGE), which is found on the surface of the cell[75].RAGE activation starts the pathways for MAPK (mitogen-activated protein kinase) and nuclear factor kappa B (NF-κB)[78].ROS (reactive oxygen species) generation may be elevated by AGEs[82].ROS have the ability to trigger or facilitate MAPK pathway activation[83]. Glutamine:fructose-6-phosphate amidotransferase (GFAT), a precursor and speed-limiting enzyme in the hexosamine biosynthesis cycle, catalyzes the transformation of fructose-6-phosphate into glucosamine-6-phosphate. UDP-N-acetylglucosamine (UDP-GlcNAc) is the main byproduct[86].Increased expression of transcription factors like TGF-α and TGF-ß, which prevent mesangial cell mitogenesis and promote collagen matrix and basement membrane thickening, has been linked to changes in gene expression and hyperactivity of the O-glucosamine-N-Acteyl transferase enzyme and hexosamine pathway. All of these contribute to the hexosamine pathway's pro-oxidative and toxic effects in diabetes[87]. The body produces more reactive oxygen species (ROS) than its antioxidant defenses can handle can eliminate, leading to oxidative stress (OS)[88].The process how lipids containing carbon-carbon double bonds, especially polyunsaturated fatty acids (PUFAs), are targeted by oxidants like free radicals or nonradical species, involves abstraction of hydrogen from an introduction of carbon and oxygen, producing peroxyl radicals in lipids and hydroperoxides as previously explained. This is known as lipid peroxidation [89].The presence of oxidative stress has been shown to contribute to the development of aggregation of α-syn. The development of soluble α-syn oligomers is an important step in the pathophysiology of Parkinson's disease [90].Changes in mitochondrial biogenesis brought on by transcription factor dysregulation may result in mitochondrial malfunction, which would negatively impact cellular bioenergetics. In white blood cells and substantial nigra (SN) of PD patients' postmortem brains, PGC-1α levels are reduced [91].

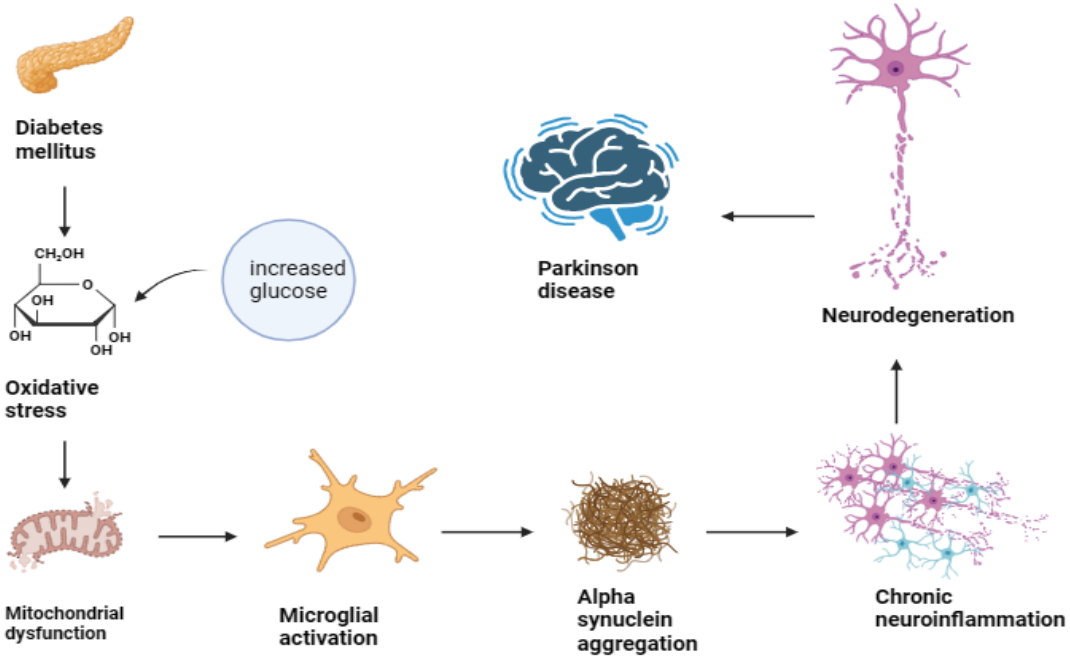

Fig 2: - Mechanistic pathway linking diabetes mellitus to Parkinsonism.

The pathogenesis of idiopathic Parkinson's disease now indicates that most DA-neuronal tissue damage is mediated by the persistent production of mediators of inflammation by microglial cells, namely the formation of NO and ROS by microglia that are activated[92]. Deramification—the change to an amoeboid state—has been seen as a sign of microglial activation. Nevertheless, numerous investigations have demonstrated that microglia in their supposedly "resting" state—which is typified by an enormously ramified morphology—are actually incredibly dynamic and active[97].The presence of Pathogen-Associated Molecular Patterns (PAMPs), which are highly conserved in microorganisms, and/or by the presence of injured cells DAMPs are produced and include weakly folded proteins, peptide aggregates, and nucleic acids that are present in neurodegenerative diseases, can activate the Patterns-recognition receptors (PRRs) that microglia are equipped with[93].While the TRIF-dependent pathway is triggered TLR3 signaling, which usually results in the nuclear factor (NF)-κB activation. On the other hand, both paths concurrently activate TLR4[94]. Proinflammatory TNF, IL-6, and interleukin (IL)-1β are examples of cytokines that occur in high concentrations in patient serum, cerebrospinal fluid, and brains. Thus, microglia and other invading peripheral myeloid cells are the primary generators of such cytokines that trigger inflammation in the brain[95].Proinflammatory cytokines are crucial for facilitating the astrocytic activation of active microglia (the release of cytokines that promote inflammation from microglia is a hallmark of their activation)[96].Reactive astrocyte formation and Parkinson's disease pathogenesis are significantly influenced by the stimulation of nuclear factors kappa-B (NF-κB), a crucial mediator of neuroinflammation. Astrocytic ROS/RNS production and inflammatory substances cytokine release are markedly increased by NF-κB overexpression, which starts a harmful feedforward cycle of prolonged inflammation with astrocytic oxidative/nitrosative stress that ultimately results in neurotoxicity[98].α-syn misfolding and mitochondrial malfunction are among the conditions that cause persistent neuroinflammation[99].Persistent activation of astroglial and microglial cells is linked to Parkinson's disease (PD) either directly or indirectly through the disease's progression[100].The pathogenesis of Parkinson's disease and the disruption in the blood–brain barrier are significantly influenced by neuro-inflammation. Neurotoxicity and dysfunction in neurons result from underlying inflammatory processes, such as the activation of glial cells, like those microglia and astrocytes, which sets off the creation of pro-inflammatory cytokines[101].It is thought that neurons producing dopamine are especially susceptible to oxidative damage owing of their high iron concentration, poor antioxidant levels, and rapid oxygen metabolism[102].When combined, neuroinflammation and oxidative stress support one another's growth while carrying out their individual roles and work in concert to cause and exacerbate Parkinson's disease[103].The establishment of this vicious loop may serve a critical function in the gradual degradation of dopaminergic nerve cells in PD[104].Constipation, urinary dysfunction, melancholy, psychosis, apathy, and sleep disruption are the most prevalent non-motor symptoms of Parkinson's disease[106]. Fig 2 illustrates how chronic hyperglycaemia, mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired

dopaminergic neuron survival collectively contribute to the advancement and progression of parkinsonism in individuals with diabetes mellitus.

4. TREATMENT:-

4.1. ANTIOXIDANTS:-

Individuals who are nutritionally deficient in antioxidant substances, such as selenium, folic acid, and vitamins A, C, E, as well as niacin, are more likely to develop Parkinson's disease. endogenous antioxidants like glutathione and coenzyme Q10 (CoQ10) are not present in high concentrations in the brains of PD patients [79] Inflammatory cytokines, ROS-induced toxicity, and ROS levels have all been successfully reduced by attenuating ROS generation[77].Therefore, supplementation with antioxidants may prevent or reduce the rate of progression of this disease [81] By directly scavenging ROS, attaching to anti-oxidant enzymes like cofactors, and controlling genes that govern intracellular antioxidant systems, phytochemicals, minerals, and vitamins demonstrate their antioxidant qualities [84] Antioxidants block further oxidation events by being oxidized themselves and stop these chain reactions by eliminating free radical intermediates [110] Nutritional antioxidants, particularly vitamin E and polyphenols, have been shown in studies to prevent neuronal death in vitro and may have therapeutic benefits in animal models with neurodegenerative illnesses including AD and PD.[108] Due to their many health advantages and ability to be found in foods and supplements, natural antioxidants like polyphenols are growing in popularity [80] By protecting neurons from oxidative stress or as amyloid-β neuronal damage, polyphenols, like some flavanones, can directly shield or stimulate neurons by bridging the blood–brain barrier [107] By triggering antiapoptotic pathways aimed at mitochondrial malfunction and produce neurotrophic factors, flavonoids demonstrate a neuroprotective impact besides their anti-inflammatory and antioxidant properties.[109] The majority of vitamin C is found in neuron-rich regions. Second, SVCT2 can carry vitamin C to the brain, while GLUT1 and GLUT3 can carry DHA to the brain[85]By scavenging reactive oxygen species (ROS), reducing mitochondrial dysfunction, and halting neuronal apoptosis following neurotoxic shocks that resemble neurodegenerative diseases, vitamin E has potent antioxidant qualities.[105]Reactive oxygen species (also called ROS are neutralized, and antioxidant enzyme production and activity are increased, as part of the melatonin mechanism.[111]The RORα pathway is inhibited in the increase in antioxidant enzyme activity brought on by melatonin[112].

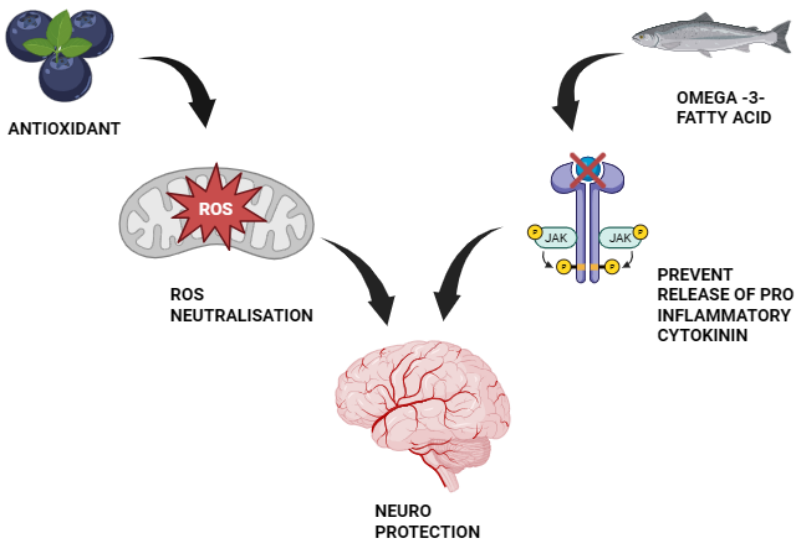

Fig 3:- Neuroprotective mechanisms of antioxidants and omega-3 fatty acids

4.1.1. OMEGA-3- FATTY ACID:-

In Parkinson's disease, ω-3 PUFAs may have a neuroprotective impact.[114] By preventing the release of proinflammatory cytokines, increasing the expression of neurotrophic factors, restoring the function of mitochondria and membrane fluidity, lowering oxidant production levels, and preserving α-synuclein proteostasis, n-3 PUFAs may help people with Parkinson's disease.[113] By reducing neuroinflammation and maintaining dopaminergic neurons, polyunsaturated fatty acids (PUFAs) have protective properties such as anti-inflammatory, anti-apoptotic, and antioxidant activity. They may also hold promise for postponing or preventing Parkinson's disease[115].The fatty acid content of phospholipids found in neuronal cell membranes is influenced by dietary fatty acid intake. Through their effects on receptor systems and ion channel activities, fatty acids can modify electrical signal transduction pathways.[119] In supplementary to UPDRS, the addition of omega-3 using linseed oil along with vitamins E had positive effects on glutathione, the overall antioxidant capacity (TAC), high-sensitive C-reactive protein (hs-CRP), and indicators of insulin metabolism.[120]By boosting long-term potentiation, n-3 fatty acid exposure increases adult hippocampus neurogenesis linked to cognitive and behavioural functions, modifies synaptic protein expression, and fosters synaptic plasticity[122]. Fig 3 illustrates how reactive oxygen species are neutralized by dietary antioxidants, while omega-3 fatty acids inhibit the release of pro-inflammatory cytokines via modulation of inflammatory signalling pathways. Together, these mechanisms contribute to enhanced neuroprotection and mitigation of neuroinflammatory damage.

4.2. PRASINEZUMAB:-

The epitope located in the carboxyl end of human alpha-synuclein is the target of the human-derived mab immunoglobulin G1 antibody known as Prasinezumab (formerly known as RO7046015/PRX002). Human aggregated alpha-synuclein is bound by it with great avidity and affinity [125].A phase II, randomly assigned, double-blind, placebo-controlled investigation called PASADENA examines the safety and effectiveness of Prasinezumab in the initial phases of Parkinson's disease [129].PRX002, which targets α-synuclein aggregates in both soluble and insoluble forms[126].Several in vivo as well as in vitro α-synucleinopathy models have been used to demonstrate the effects of PRX002 murine homologue (9E4). Specifically, 9E4 prevented α-synuclein from being transmitted from cell to cell, decreased intracellular α-synuclein pathology, prevented synaptic loss and gliosis, and improved cognitive and motor behavior deficits[127].According to the study, the antibody's passive delivery reduced intracellular α-synuclein pathology, prevented cell transmission, and corrected motor and cognitive impairments[128].In accordance with preclinical research, Prasinezumab lowers neuropathology and improves behavioral outcomes by reducing a neurotoxic, shortened version of α-syn and blocking its propagation between cells[132].Phase I trials on healthy volunteers and individuals with Parkinson's disease showed positive outcomes of brain penetration and target engagement (dose-dependent decrease in α-synuclein concentrations in free serum after treatment)[130].PASADENA results led to the decision to carry out further research into Prasinezumab's potential as a treatment.In order to assess the safety and effectiveness of Prasinezumab versus placebo in individuals with early-stage Parkinson's disease (PD) receiving stable symptomatic PD treatment, a new Phase 2b experiment called PADOVA was started[131]. Fig 4 illustrates how the monoclonal antibody Prasinuzemab binds extracellular
α-synuclein aggregates at the synaptic cleft, forming an antibody–α-synuclein complex. This complex is subsequently recognized by microglial Fc receptors, facilitating its uptake and removal through endocytosis. This targeted clearance aims to reduce pathogenic α-synuclein burden and mitigate neurodegeneration in Parkinson’s disease.

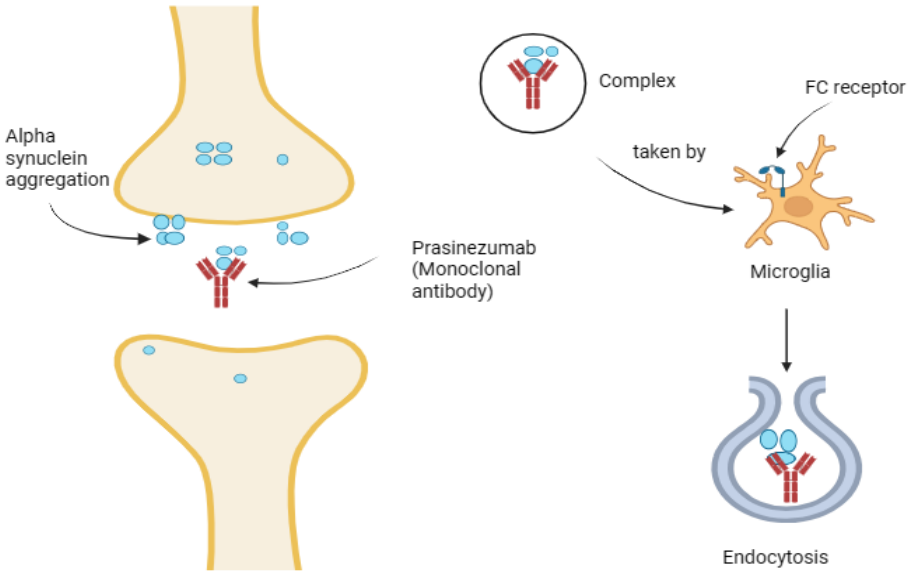

Fig 4:- Mechanism of Prasinuzemab-mediated clearance of α-synuclein aggregates.

4.3. DEEP BRAIN STIMULATION:-

Deep brain stimulation, or DBS, is a functional neurosurgery technique that involves continuously stimulating a neural brain structure with electricity through electrodes that are permanently implanted attached to an integrated neuro pacemaker or stimulator[116]. The subthalamic nucleus (STN) DBS for Parkinson's disease (PD) relieves tremor over seconds, less serious axial indications over hours or days, including rigidity and bradykinesia spanning minutes to hours[117].It's still unclear how DBS regulates motor symptoms, but it probably involves both network-wide impacts on pathogenic oscillatory activity and local consequences on neuronal firing patterns. Apart from providing efficient alleviation of motor symptoms, new data from preclinical models indicates that long-term DBS might also restrict motor dysfunction and guard against neuronal death[118].According to a recent meta-analysis, STN-DBS improves motor function more effectively than GPi-DBS(globus pallidus interna)[121].Additionally, DBS in the initial phase of motor PD may delay the disease's course, thus avoiding the emergence of late-stage comorbidities and improving overall quality of life, according to some research[123].Although both STN as well as GPI DBS enhance motor performance, the choice of target should be tailored to the person based on variations in nonmotor results[124].Bilateral STN-DBS or GPi-DBS has been found in numerous studies to significantly improve patients' motor control with advanced Parkinson's disease[133].

5. CONCLUSION:-

The increasing amount of data that connects prolonged diabetes mellitus towards a higher risk of Parkinson's disease emphasizes how important common pathogenic processes like neuroinflammation and oxidative stress are. Chronic diabetes-related hyperglycemia encourages systemic inflammation, mitochondrial dysfunction, and elevated reactive oxygen species production, all of which can exacerbate the dopaminergic neuronal degeneration that characterizes Parkinson's disease. Early detection and disease modification are made possible by the recognition of this integrated route. Promising approaches to treating Parkinson's disease among individuals with previous cases of diabetes include the usage of antioxidants to reduce oxidative stress, brain stimulation in order to alleviate motor symptoms, and new disease-modifying drugs like Prasinezumab that target α-synuclein aggregation. The goal of future studies should be to better understand the molecular connections and enhance these therapeutic strategies in order to slow or stop the development of neurotoxicity in this vulnerable group.

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