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Is cholesterol a contributing factor to Parkinson's disease? A review

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ABSTRACT: The study was undertaken to report any relationship between cholesterol and Parkinson's disease (PD) and to identify if cholesterol is a contributing factor to the progression of PD, a slow progressive neurodegenerative disorder, which affects almost 1-2 % of the population above the age of 60 years. PD is mainly idiopathic in nature and is characterised by bradykinesia, resting tremor, muscular rigidity, gait disturbances and postural reflex impairment. Cholesterol is required for the synthesis of steroid hormones, bile acid and for the formation of lipid rafts. Thus deficiency of cholesterol may affect signalling and synaptic transmission of brain. As lipoprotein cannot cross the blood-brain barrier, cholesterol is mainly synthesised *in situ* from endogenous and exogenous plasma protein. In this study, we had collected about 100 of standard articles with the help of PubMed search engine. A number of case control studies have reported an association between low LDL-C and higher occurrence of PD. Also the use of cholesterol lowering drugs were found to be associated with lower occurrence of PD. Based on a systematic review, it may be concluded that the APOE e2 allele had a positive association with sporadic PD, resulting in higher prevalence of sporadic PD. Moreover, APOE e2 allele has always been associated with lower plasma LDL-C. From the appraisal of articles, it may be concluded that lower the cholesterol (LDL-C) level, the risk of PD is increased. Lower levels of LDL-C were also linked to higher mortality and higher incidence of other neurodegenerative disease like AD.

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INTRODUCTIONS:

Parkinson's disease (PD) is a slow progressive neurodegenerative disorder, which affects almost 1-2% of the population above the age of 60 years. The risk of PD is higher in men than in women. PD is mainly idiopathic in nature. PD is characterised by bradykinesia, resting tremor, muscular rigidity, gait disturbances, and postural reflex impairment [1-3]. The pathological changes are characterized by loss of substantial nigra

and dopaminergic input as a result it affects the neurotransmitters and also genetic factors play a key role [4,5]. PD is mainly caused due to abnormality in basal ganglia which include neo-striatum, the external and internal pallidal segments (GPe, GPi), the subthalamic nucleus (STN), and the substantia nigra with its pars reticulata (SNr) and pars compacta (SNc). They involve the specific thalamic and cortical area [6]. The motor symptoms of PD occur long before the non-motor symptoms. The symptoms occur after the degeneration of substantial nigrostriatal neuron. The dopamine loss in the basal ganglia activates the secondary morphological changes [7]. The depletion of dopamine causes changes in the density and sensitivity of the dopamine receptors. Studies had showed an increased mRNA expression for D2-receptor sites in the striatum of PD patient [8].

Abnormality in the oscillatory pattern was seen in the PD patient within the single cell level to the neural elements [9]. The degeneration of dopaminergic SNc neurons and their projections to the striatum evolves very slowly in PD patients. The limbic portions to the striatum degenerate slowly over time are a slowly evolving process that may take decades to develop. SNc projections to the putamen degenerate earlier than projections to associative or limbic portions of the striatum. Other pathological changes such as reduction in the density of dendritic spines on MSNs in the putamen [10]. The functional imaging and positron emission tomography (PET) in a PD patient shows reduced cortical activation especially in the supplementary motor area (SMA) and in the anterior cingulate cortex [11-15]. PD patients show motor impairment and abnormal cognitive performance which is caused due to dopamine loss in the non-motor area of striatum [16].The loss of dopamine causes disruption in the frontal and cerebral cortex which receive direct input from basal ganglia. In PD patients EEG shows abnormality in beta-band associated with cortical networks [17,18]. When dopamine depletion occurs, the association between the neighbouring basal ganglia cells and nucleus increased. It was observed that when dopaminergic agents are administered inter neuronal synchrony is reduced and with an increased electro coupling the synchrony can be increased [19].

Cholesterol:

Changes in cholesterol homeostatics in human brain is linked to neurodegenerative diseases like Alzhemier's disease (AD), Huntington's disease (HD), PD, etc. Cholesterol consists of cholesterol esters, phospholipids or triglycerides. AD includes neuro fibrillary tangles (NFTs) and senile plaques formed by deposition of abnormal tau filaments and extracellular deposits of β-amyloid fibrils.

Cholesterol is required for the synthesis of steroid hormones, bile acid and for the formation of lipid rafts. Thus deficiency of cholesterol may affect brain and its signalling and synaptic transmission. Cholesterol is mainly synthesised from endogenous and exogenous plasma protein. Since lipoprotein cannot cross the blood-brain barrier (BBB), the cholesterol in brain is synthesized in situ. The total body cholesterol is approximately 25 % and among that 2-5 % of cholesterol is made by the brain. In the central nervous system (CNS), 70-90 % of cholesterol is distributed within the axons and myelin and helps in transmission of electrical signal. The apolipoprotein E (APOE) along with the cholesterol produces structures similar to high density lipoproteins and are up taken by the neurons. The cholesterol is altered between the astrocytes to the neurons and this interaction is very important for the normal neuronal functioning. APOE plays a key role in cholesterol homeostasis and distribution among the brain cells. Cholesterol helps to modulate α-synuclein aggregation. Some studies suggest that people with an increased plasma concentration are in an increased risk of developing PD [20]. Cholesterol derivatives such as 27-hydroxycholesterol decreases the dopamine synthesis and increases the α-synuclein level by the activation of receptors in the liver [21, 22].

***De novo* cholesterol synthesis:**

This process begins with the transformation of an acetyl-CoA into 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) with the help of HMG-CoA -synthetase and it is converted to mevalonate with the help of HMG-CoA reductase. This process is irreversible and rate – limiting step in the biosynthesis of cholesterol, the main 2 pathways are represented in (Fig 1).

The sterols in the neurons are synthesized through the Kandutsch-Russel cholesterol synthetic pathway (7-dehydrocholesterol, lanosterol), and astrocytes contain precursors of the Bloch pathway (desmosterol). The cholesterol present in the endoplasmic reticulum varies than those in the plasma membranes and this influences the total body cholesterol.SREBP (sterol-regulatory element-binding protein) is the main regulator of the cholesterol which helps in the binding to SCAP (SREBP

cleavage-activating protein), which act as a cholesterol detector. When there is high cholesterol concentration the preservation of SREBP-2/SCAP complex occurs due to retention of INSIG-1 and -2 (insulin-induced protein 1 and 2). Inside the cell the SCAP releases the N-terminal domain of SREBP-2, which is then translocated in order to bind to sterol regulatory elements (SRE) within the genes which codes for biosynthesis of cholesterol [23-25].

Role of cholesterol in brain:

Cholesterol is one of the main lipids, with about 23-25% present in brain cells. Within the CNS the cholesterol has many important functions like maintaining the nerve conduction, signal transmission and to obstruct the growth of dendrites [26,27]. The BBB prohibits the uptake of lipoproteins from the circulation. Within the brain above 95% of cholesterol is synthesised by glial cells. Aging and neurodegenerative disorder may impair the BBB [28, 29].There are two major cholesterol stores in the brain, the smaller one made by the plasma membranes of neurons (10 %) and the glial cells (20 %). The larger pool accounts for (70 %) in the myelin, with a slower turnover. During the period of active myelenation, cholesterol synthesis is very high. The plasma concentration of oligodendrocytes is increased to 10 fold during the generation of myelin sheath. After the myelination the cholesterol synthesis is decreased up to 90 %. The cholesterol within the neuron plays a fundamental role in the propagation and differentiation of axons and dendrites. The brain-derived neurotrophic factor (BDNF) enhances the neuronal cholesterol synthesis. Astrocyte derived cholesterol is essential for substantial synapse formation. Overall the neuronal cholesterol synthesis is crucial for developing brain [30].

DISCUSSION:

Xuemei Huang, *et al*. summarizes that low-density lipoprotein-cholesterol (LDL-C) were associated with higher prevalence of PD. A case control study was conducted with 124 PD cases from a tertiary movement disorder clinic as case and 110 controls from the spouse population of the same clinic. From the case control study it was found that there is an association between low LDL-C and higher occurrence of PD. Also the use of cholesterol lowering drugs was found to be associated with lower occurrence of PD. That is statin use may lower PD occurrence [31]. Based on a systematic review it was concluded that the APOE e2 allele has a positive association with sporadic PD, resulting in higher prevalence of sporadic PD [32]. Moreover, APOE e2 allele has always been associated with lower plasma LDL-C [33,34]. It was also reported that there is low cholesterol biosynthesis in patients with PD than in controls [35].LDL-C is associated with increased risk of PD in Japanese–American men after age-adjustment. The relationship of lower LDL-C with PD was clearly stronger in the younger-aged men (age <75) and the risk of PD seemed to decline with rising LDL-C levels in those who were older. This finding is consistent with increasing etiological heterogeneity with age [36, 37].

A study of the Rotterdam cohort conducted in women found an association between the lower total cholesterol and increased PD risk. A prospective population based study was conducted with proper follow up and it was found that higher serum levels of total cholesterol were associated with a significantly decreased risk of Parkinson's disease. The association was restricted to women and remained unchanged for additional adjustments of smoking, dietary vitamin E, coffee consumption, body mass index, APOE genotype, and baseline use of lipid-lowering drugs .Since the serum cholesterol level were measured before the onset of Parkinson's it is unlikely that the relation between serum cholesterol and PD risk as a complication of PD [38]. According to a prospective study conducted by the Honolulu Heart Program 58 PD cases was identified during a 26 year follow up and had 8006 Japanese-American men from Hawaii. A reverse association was found between LDL cholesterol and PD risk in an updated analysis by the Honolulu Heart Program among 3233 subjects [39,40]. A large prospective analysis found that high cholesterol may increase PD risk. This cohort study included 24,733 Finnish men and 26,153 women aged 25-74 years without history of PD and stroke at baseline. During a mean follow-up period of 18.1 years, 321 men and 304 women developed incident PD and the average ages at the time of diagnosis were 64.5 years in men and 65.8 years in women. The Finnish study also shows a positive association between total serum cholesterol and BMI, though the study was conducted independent of BMI at baseline [41].An association between excess weight and PD risk was found by the Honolulu Heart Program [40].

According to Simon, *et al*. altogether the risk of PD was not associated with the updated history of hypertension, hypercholesterolemia and diabetes but there was a moderate decrease with increase of blood cholesterol

levels. It was seen during the follow period that there were 530 incident cases of PD, including 264 in women (average age at diagnosis of 63.5 years) and 266 cases in men (average age at diagnosis of 69.7 years).In this case study, it was noted that individuals with hypertension, hypercholesterolemia and diabetes were less physically active and had higher BMI than those without these conditions. But risk of PD had decreased with the elevating levels of self-reported cholesterol. Also there was no association with PD risk and use of cholesterol lowering drugs [42].

Based on a retrospective case control study conducted on 178 freshly diagnosed idiopathic Parkinson (IPD) patients and 533 controls with other neurological conditions it was reported that diabetes, history of smoking, high blood pressure, high blood glucose, high blood cholesterol and triglycerides were less frequent in IPD patients than in controls. This study interprets that the association of untreated IPD with reduced vascular diseases risk factors can be credited to reduced autonomic activity and also suggests about the possible role of autonomic hyperactivity in the pathogenesis of vascular disorder [43].

CONCLUSION:

From the appraisal of articles it is concluded that lower the cholesterol level especially LDL cholesterol, the risk of PD is increased. Lower levels of LDL-C are also linked to higher mortality and higher incidence of other neurodegenerative disease like AD. The Rotterdam cohort study found the coalition between the lower LDL-C and PD in women.

Huang, *et al*. studies founded a stronger association between lower LDL-C and PD in younger male population. With a gradually increasing level of LDL-C it was observed a gradual decline in risk of PD in older patients even though the dose-response relationship is not significant. The deprivation of nigral neurons may cause decreased cholesterol biosynthesis. The recent meta-analysis emphasised on the increased risk of PD in carriers of the APOE e2 allele. APOE e2 allele is related to lower plasma total cholesterol levels. In another prospective cohort study it was found that with a higher intake of polyunsaturated fatty acids the risk of PD decreases.

BBB is impermeable to cholesterol containing lipids therefore most of the brain cholesterol is synthesised within the CNS and the effect of serum cholesterol on the brain cholesterol remains unclear. Another hypothetical explanation is that the serum cholesterol is a prominent source for the determination of serum concentration coenzyme Q10 which acts as powerful endogenous antioxidant and both the cholesterol and coenzyme Q10 is derived from same biosynthetic pathway. Within the plasma the coenzyme Q10 is incorporated to the low density lipoproteins which make coenzyme Q10 as a potential agent for the treatment of PD. Other studies in male population conclude with a lack of association between cholesterol and risk of PD which is due to weaker correlation between cholesterol and coenzyme Q10. According to some studies there is a larger variation in cholesterol level between male and female population which may be due to use lipid modifying agents like oestrogen.

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