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Abstract

According to the World Health Organization (WHO), there are approximately 55 million people worldwide that are currently diagnosed with dementia.[2] Informal caregivers, such as family and friends, of people living with dementia (PLWD) cover more than 50% of the total cost of caregiving.[2] Apart from the cost, caregivers to PLWD also spend a significant amount of time (four hours) every day caring for dementia patients.[2] This leads to a significant amount of financial, emotional and social stress on a daily basis which has been shown to lead to an exaggerated proinflammatory response and increased blood and serum levels of Interleukin-6 (IL-6), a tightly regulated cytokine. IL-6 binds to the IL-6 receptor, leading to the homodimerization of transmembrane gp130 and thus initiating a signaling cascade that eventually leads to a proinflammatory response. Excessive proinflammatory markers, such as IL-6, can affect the profibrinolytic and anticoagulant effects of endothelial cells, leading to an increased likelihood of cardio-cerebrovascular diseases (CCVDs), such as heart failure (HF), myocardial infarction (MI), ischemic stroke (IS), and atherosclerosis. Therefore, an intervention for caregivers to PLWD may be helpful in mitigating caregivers' risk of developing cardio-cerebrovascular diseases, but further research is necessary to establish causation. This paper reviews literature that explores the association between IL-6 levels and caregiving status of individuals. Topics covered will include rates of IL-6 increase in caregivers, persistence of IL-6 increase post-caregiving, and potential interventions to reduce IL-6 levels in caregivers to PLWD.

Keywords: dementia, caregiving, IL-6, cardiovascular, cerebrovascular

Introduction

Dementia is the acquired loss of cognitive functioning in multiple cognitive domains that interferes with day-to-day activities.[1] In 2019, dementia cost the global economy approximately 1.3 trillion US Dollars.[2] Of the 1.3 trillion USD, approximately 16% was attributed to direct medical costs, 34% was attributed to direct social sector costs, and 50% was attributed to informal caregivers (such as family and friends) that spend approximately four hours per day caring for the dementia patients.[3] This large toll is partly due to the increasing number of dementia cases worldwide. According to the World Health Organization (WHO), there are approximately 55 million people worldwide that have been diagnosed with dementia.[2] These numbers are predicted to increase exponentially over the next few decades as we face an aging population worldwide.

However, some of the most overlooked problems in the field of dementia caregiving are the physiological effects that informal caregivers face

when caring for dementia patients. Informal caregivers are those that provide care to family and friends, usually for no payment. These informal caregivers of people living with dementia (PLWD) face financial, social, and emotional challenges on a daily basis as they care for their loved ones. These recurrent stressors may lead to an increased level of proinflammatory biomarkers, such as IL-6, which can lead to a myriad of health problems. 14% of the informal caregivers of PLWD are their elderly spouses, further exacerbating the physiological health consequences of caregiving due to old age.

Interleukin-6 or IL-6 is a tightly regulated proinflammatory cytokine that is quantified from blood and serum samples. It is usually present in low levels in healthy individuals, but is present in high levels in those with chronic stress. It is a multifunctional glycoprotein that is approximately 184 amino acids long and weighs 26 kDa.[4] It is produced by mononuclear macrophages, T helper 2 cells, B cells, vascular endothelial cells, smooth muscle cells and fibroblasts.[5] IL-6 binds to the IL-6R (IL-6 receptor), a cell surface receptor, which then starts a signaling cascade. The binding activates the gp130 transduction complex, causing gp130 dimerization.[5] This leads to Janus kinase (JAK) activation, which then causes phosphorylation of signal transducers and activators of transcription (STAT).[5] gp130 dimerization also causes recruitment of SH2-containing protein tyrosine phosphatase 2 (SHP2), which activates phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways.[5] These lead to a variety of downstream events, including acute phase response (response to local or systemic disturbances caused in its homeostasis) , infection defense and metabolism, including glucose homeostasis. Indeed, chronically high levels of IL-6 have been associated with higher levels of mortality.[6]

Inflammation is one of the main mechanisms used by the body to counter infections, tissue injuries and stress. However, if the inflammatory response becomes prolonged and out of control, it can lead to the accumulation of cytokines, releasing toxic substances that can lead to cell death. Excessive inflammatory responses also affect the anticoagulant and profibrinolytic ability of endothelial cells. Therefore, high levels of IL-6, a proinflammatory cytokine, over long periods of time can lead to a range of physiological changes, such as enhanced angiogenesis and hypertension.[7,8]

Past research has suggested a strong link between higher IL-6 levels and incidence of heart failure (HF), myocardial infarction (MI), ischemic stroke (IS), atherosclerosis and other cardio-cerebrovascular diseases (CCVDs).[5] CCVDs are conditions that involve restricted flow of blood to a particular part of the body (usually the heart and brain) due to narrowing of the blood vessels, formation of clots, or blockage and rupture of blood vessels.[9] Zhang et al. treated rats with acute myocardial infarction (AMI) with simvastatin, a drug that reduces IL-6 levels, leading to a reduction in collagen deposition in noninfarcted myocardium and improvement in cardiac function.[10] Additionally, Biasucci et al. demonstrate that IL-6 levels are elevated in patients with an unstable angina, further suggesting an association between IL-6 and CCVDs.[11] Research has suggested that this link between IL-6 and CCVDs may be mediated by increased production of C-reactive protein (CRP) in the liver. This, in turn, leads to the recruitment of leukocytes and thrombosis which increases the risk for developing CCVDs.[5]

High IL-6 levels known to be associated with many different types of stress. However, for the premises of this paper, we will focus only on the correlation between high IL-6 levels and caregivers to people living with dementia.

Caring for family members with dementia can cause informal caregivers, including family and friends, to experience fatigue and chronic stress. This may lead to increased levels of IL-6 over long periods of time, which, as discussed above, can be detrimental to the person's health. This paper aims to describe recent research on the association between IL-6 and informal caregiving for dementia

patients and to discuss past studies which have assessed psychosocial interventions to reduce IL-6 and potential future directions for the field.

Methodology

The first part of the paper focuses on the association between IL-6 levels and caregiving for dementia patients. Due to the low number of research studies performed specifically on this relationship, not many limitations could be applied while researching studies relevant to this paper. However, only studies conducted in the last 25 years were considered for this review. In addition, only studies measuring IL-6 levels in caregivers of dementia patients were considered. It was also ensured that all studies had non-caregivers as the control group. The second part of this paper focused on discussing research studies that tested interventions to reduce IL-6 levels in caregivers to dementia patients. Again, due to the lack of much research in this field, not too many limitations could be applied for this review. Only studies in the last 15 years (since 2009) were considered for this review. In addition, only papers that tested interventions specifically on caregivers to dementia patients were included in this review. Lastly, only studies that used IL-6 levels as a measure of intervention efficacy were included in the review.

1. Association of IL-6 levels and Caregiving for Dementia Patients

Past research has suggested a link between negative and stressful emotions and production of IL-6 levels. Recurrent stressful experiences can cause dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which controls the stress response, and leads to an exaggerated production of IL-6. Caregivers for dementia patients are expected to have higher levels of stress due their caregiving activities and the behavioral symptoms of dementia patients, such as sleep disturbances and agitation. Hence, it is expected that caregivers of dementia patients may have significantly higher levels of IL-6 compared to non-caregivers. In the following section, this paper reviews studies that explore the association between IL-6 levels and caregiving for dementia patients.

1.1 Number of Stressors and Caregiving Status

Gouin et al. (2012) conducted a cross-sectional study that included 53 caregivers and 77 controls (non-caregivers).[12] It measured the number of daily stressors that each participant had experienced over the past 24h and collected blood samples to detect serum IL-6 and CRP levels.

Results suggested that caregiving status was significantly associated with the report of multiple stressors compared to the absence of stressors in the past 24h. Approximately 50% of the caregivers reported multiple daily stressors compared to approximately 25% of non-caregivers.[12] However, caregiver status was not significantly related to the presence of one stressor or no stressors in the past 24h. This means that caregivers were more likely to have reported multiple stressors in the past 24h, but not more likely to have reported one stressor or no stressor compared to non-caregivers.

Results also found that the number of daily stressors was related to IL-6 levels regardless of caregiving status. Those participants that had experienced multiple stressors in the past 24h were measured by blood samples to have higher IL-6 levels than those that experienced zero stressors. Their IL-6 levels were also higher, although not significantly, than those that had reported just one stressor in the past 24h. This suggests that IL-6 levels were, in fact, positively associated with the number of stressors.

However, the study did not show a significant association between caregiving status and IL-6 levels. Caregivers were more likely to report multiple daily stressors, yet still did not have significantly higher IL-6 levels compared to non-caregivers. This is contradictory to the understanding that stress is correlated to elevated levels of IL-6 that other studies show. For example, Carpenter et al. reported that early childhood stress leads to higher IL-6

concentrations over time.[13] One reason for this discrepancy in results may be due to the differences in timing of measurement of IL-6 concentrations. In this study, the IL-6 levels were only measured over 24h and a better understanding of the association between caregiving status and IL-6 may be yielded by measuring proinflammatory marker levels over multiple days.

The study did, however, show a significant relationship between caregiving status and CRP levels. Caregivers were measured to have higher CRP levels than non-caregivers. These results are again puzzling because IL-6 stimulates the hepatic synthesis of CRP, but this study did not show an association between caregiving status and IL-6.[14] This also suggests the need to increase the number of IL-6 measurements taken in future studies. However, since CRP is a marker of atherothrombotic vascular disease, this study does support the overarching hypothesis that caregiving for dementia patients is associated with higher risk of CCVDs in caregivers.

1.2 Effect of Gender and Dementia Severity on IL-6 levels

Mills et al. (2008) explored the effects that gender and dementia severity have on IL-6 levels in spousal caregivers of dementia patients.[15] It aimed to examine whether one gender was at a higher risk from caregiving and whether caring for a patient with more severe dementia led to greater IL-6 levels. 81 caregivers and 41 non-caregivers were included in the study.[15]

Consistent with expectations, dementia caregivers reported significantly greater frequency, severity and distress from behavioral symptoms of dementia patients compared to non-caregivers. Results also suggested that dementia caregivers caring for spouses with moderate to severe dementia reported higher frequency, severity and distress from behavioral symptoms compared to caregivers caring for spouses with questionable to mild dementia. Analyses also suggested that IL-6 levels were higher in male and female caregivers for spouses with moderate to severe dementia compared to non-caregivers.

The study results also showed that females had significantly higher levels of role overload stress (stress that is caused by one's perception of the demands of caregiving exceeding the available resources) compared to males. However, contrary to this, IL-6 levels were elevated up to 28 to 38% in males caring for spouses with moderate to severe dementia (high CDR) compared to other caregivers.[15] These higher IL-6 levels in males may be due to the results found that male caregivers spent more time awake after sleep onset than female caregivers caring for dementia spouses with moderate to severe dementia. This poorer sleep outcome in male caregivers may lead to increased IL-6 levels and worse physical functioning.[16]

This study indicates that more research is needed to look at the differences in the coping strategies employed for caregiving stress by male and female caregivers. This will provide more insight into the understanding of role overload stress and IL-6 level differences seen in this study between males and females. Additionally, only one IL-6 level measurement was taken. Future studies should include more IL-6 measurements over several days to better understand the role that gender and dementia severity plays on IL-6 levels in spousal caregivers of dementia patients.

1.3 Longitudinal Study to Explore Association of IL-6 Levels and Caregiving Status

Unlike the studies discussed earlier, Kiecolt-Glaser et al. (2003) observed the IL-6 levels in caregivers over a period of 6 years.[17] As mentioned before, a longitudinal study enables researchers to better understand the pattern of IL-6 in relation to the chronic stress due to caregiving. The study analyzed IL-6 levels from plasma samples of those caregivers that were at least 55 years old and had at least two samples across six consecutive years.[17] The dementia patients of multiple caregivers died over the 6 years, which provided new insight in IL-6 levels after caregiving activity has ceased.

The study used data points to create a model of change in IL-6 levels in caregivers and non-caregivers with age as a predictor of IL-6 levels.[17] Predicted IL-6 levels were modeled to increase in caregivers at an average rate that is approximately four times greater than that of non-caregivers.[17] Results from the study also suggested that caregivers reported higher stress than controls over the 6 years compared to non-caregivers.[17] This again suggests that caregivers of dementia patients suffer from higher stress and IL-6 levels, and increases the likelihood that there is an association between caregiving status and IL-6 levels.

IL-6 data was also analyzed between two groups: one group included data from current caregivers and the other group included post-caregiving data from former caregivers (former caregivers are those individuals whose spouses with dementia died before or during the course of the study). The results found that there was no statistically significant difference in the absolute levels or average rate of change of IL-6 levels between former caregivers and current caregivers.[17] This may be explained by the understanding that chronic stress can permanently alter the inflammatory response mechanism such that subsequent stressors would produce exaggerated proinflammatory responses and hence higher proinflammatory cytokine levels.[17] This suggests that even after the caregiving ends upon the death of the family member with dementia, the physiological downsides of prolonged caregiving remain due to prolonged inflammatory responses.

The demographic data collected over the course of the study also provided some interesting results. After controlling for age, males had significantly higher levels of IL-6 than females for two out of the six years in the study. This increases confidence in the results that were discussed in the previous study (Mills et al., 2008) and provides a longitudinal look at the effect that gender plays on IL-6 levels.[15] Additionally, data also indicated that African Americans had significantly higher IL-6 levels than non-African Americans for four out of the six years of the study. These higher IL-6 levels in African Americans can be attributed to the racial and economic disparities that exist in healthcare.[18]

Overall, this study provides key longitudinal insights into the relationship between caregiving for a dementia family member and IL-6 levels. The results that IL-6 levels increased at a faster average rate in caregivers compared to non-caregivers further provides evidence to the understanding that long-term stress can worsen physiological functioning faster than normal aging. Additionally, this study highlights key populations that are at higher risk from dementia caregiving activities, including males and African Americans. Future longitudinal studies should attempt to record more IL-6 data over a longer period to better understand IL-6 level trends over time.

1.4 IL-6 levels after activation of the inflammatory response by vaccination

Segerstrom et al. (2008) looked at how chronic stress due to dementia caregiving can lead to reduced antibody production and higher IL-6 levels after influenza vaccination. The study also looked at how repetitive thoughts, which are recurrent and prolonged thoughts about oneself and one's experiences, can alter stress outcomes and IL-6 levels.[19] These repetitive thoughts can be negative (e.g., worrying) or neutral (e.g., reflection), which can alter IL-6 levels in caregivers differently. As discussed earlier in the paper, stress activates the inflammatory responses and hence leads to higher levels of IL-6. Additionally, vaccinations also stimulate the immune system, which leads to higher IL-6 levels post-vaccination in caregivers than non-caregivers.[20]

The results suggested that there was no significant difference in the levels of negative or neutral repetitive thoughts between caregivers and non-caregivers. This means that caregivers are not more likely to engage in negative repetitive thoughts than non-caregivers, despite their higher level of daily stress from caregiving.

It was found that negative repetitive thoughts were associated with higher levels of IL-6 both pre- and post-vaccination compared to neutral repetitive thoughts, but this was not a significant difference.[19] With increasing levels of neutral repetitive thought, controls saw lower levels of IL-6 post-vaccine.[19] However, with increasing levels of neutral repetitive thoughts, caregivers saw higher levels of IL-6 post-vaccine.[19] Despite the higher frequency of neutral repetitive thoughts, the inflammatory response of caregivers due to chronic stress is more prolonged, leading to higher IL-6 levels.

Results also indicated that caregivers had higher IL-6 levels pre-vaccination compared to controls, although not significantly. After controlling for pre-vaccination levels, results indicated that caregivers had significantly higher IL-6 levels at 4 weeks post-vaccination compared to non-caregiver controls.[19] This suggests that caregivers had elevations in IL-6, due to vaccinations, that were more prolonged than non-caregivers, which may be attributable to higher chronic stress due to caregiving.[19] IL-6 levels in caregivers were also seen to be independent of depression levels.

This study was crucial in suggesting the long-term physiological effect that caregiving stress had on caregivers for people living with dementia. Caregivers, despite increasing neutral repetitive thought, were shown to have higher IL-6 levels post- influenza vaccination. This may be because the caregivers' daily stressful environment and the repetitive thoughts leads to an inflammatory response and, actually, a more prolonged response. In addition, this prolonged response leads to IL-6 levels remaining higher for a longer period of time, increasing the risk of cardio- and cerebrovascular diseases. This study also clearly shows how the repetitive thought pattern of caregivers can be improved through future interventions to reduce these health risks. Future studies should aim to gather post-vaccination IL-6 data more frequently for a better understanding of the prolonged immune response.

1.5 Summary

The research studies highlighted above have been crucial in understanding how daily caregiving activities of caregivers for PLWD impact blood IL-6 levels. Results discussed earlier have indicated that caregivers face an increased level of daily stress due to their caregiving burdens and responsibilities. For example, Gouin et al. (2012) suggested that caregivers were more likely to have reported multiple stressors in the past 24h compared to non-caregivers.[12] This higher level of stress overstimulates the proinflammatory response and hence may lead to higher levels of IL-6 in caregivers.

In the 6-year longitudinal study, it was found that the IL-6 levels were increased in caregivers at a rate approximately 4 times faster than non-caregivers.[17] Additionally, studies have shown that caregivers have an inflammation response that is prolonged with the proinflammatory cytokine, IL-6, levels remaining elevated for longer. Kiecolt-Glaser et al. (2008) showed that there were no significant differences in IL-6 levels between current caregivers and former caregivers.[17] This suggests that the effects of caregiving are long-lasting, possibly due to the chronic stress permanently altering the inflammatory response, prolonging and exaggerating it.

Results from studies on dementia caregivers have also suggested that disparities do exist in the extent to which caregiving stress affects IL-6 levels. Males were reported to have significantly higher levels of IL-6 compared to females in two out of the six years in a longitudinal study.[17] In the same study, African Americans were reported to have significantly higher IL-6 levels in four out of the six years that were studied.[17]

The research studies that have been discussed so far support the understanding that caregivers for people living with dementia are burdened with a higher level of stress than non-caregivers, and hence have a higher level of IL-6. However, future studies should focus on observing the patterns of IL-6 levels with more frequent recordings. These results could

help develop new interventions to reduce the IL-6 levels of dementia caregivers and improve long-term physiological health outcomes.

2. Interventions for Dementia Caregivers

The previous section of the paper reviewed research establishing the link between stress and IL-6. Dementia caregivers, on average, tend to experience high daily stress due to their caregiving activities, and hence tend to have high IL-6 levels. These high IL-6 levels have been linked to various physiological consequences for the caregivers. For example, a study established that high IL-6 levels in dementia caregivers significantly predicted emergency department visits during a 15-month follow-up from when the IL-6 levels were measured.[21]

Due to this higher physiological risk, there is an increasing need and urgency to develop an effective intervention to reduce IL-6 levels amongst dementia caregivers. This section reviews some studies aiming to advance the development of an intervention program for caregivers of patients with dementia.

2.1 Potential Intervention Using Coping Self-Efficacy as a Tool

Mausbach et al. (2011) attempted to understand the association between coping self-efficacy (CSE) and circulating IL-6 levels in caregivers to patients with dementia in order to suggest a potential future intervention to reduce IL-6 levels.[22] Coping self-efficacy (CSE) is a measure of one's confidence in performing strategies or behaviors necessary to confront and respond to challenges.[23] Past studies have shown that CSE reduces the secretion of catecholamines, a class of neurotransmitters and hormones. Since IL-6 secretion is known to be stimulated by catecholamines, CSE may effectively reduce IL-6 levels in caregivers.

The results suggests that the relation between stress (as measured by The Role Overload scale) and IL-6 levels changes with the level of coping self-efficacy (CSE).[22] Stress was found to be significantly associated with IL-6 levels when CSE levels were low, but not when CSE levels were high.[22] When CSE was low, the plasma IL-6 levels increase with increasing levels of caregiving stress. With higher CSE, the plasma IL-6 levels decrease with increasing levels of caregiving stress. This is likely due to the self-efficacy reducing the sympathetic response to stress, hence reducing the IL-6 concentrations.[22] Caregivers with low levels of self-efficacy would have repeated, more frequent activation of the sympathetic system, leading to downstream changes that lead to higher IL-6 levels. However, caregivers with higher self-efficacy would experience less dysregulation of the sympathetic nervous system, and hence lower IL-6 levels.

These results suggest that future psychoeducational interventions for caregivers may have benefits in aiming to increase coping self-efficacy. However, future research is needed before deciding to invest further into increasing coping self-efficacy among caregivers. More studies need to be conducted to see how IL-6 levels change from pre- to post-coping self-efficacy psychoeducational intervention. Additionally, lower IL-6 levels reduce the physiological risks of caregiving. Hence, future research should also focus on exploring how coping self-efficacy interventions may help reduce caregiver cardiovascular and cerebrovascular incidents.

2.2 Pleasant Events Program (PEP) to Reduce IL-6 Levels

Moore et al. (2013) explored the efficacy of the Pleasant Events Program (PEP), a behavioral activation intervention, in reducing IL-6 levels in caregivers of dementia patients.[24] The intervention lasted six weeks. Caregivers engaged in sessions to learn how to improve their participation in leisure activities.[24] A control was also used in the study, where some participants were randomly assigned to a time-equivalent Information-Support (IS) control group, which included discussions on general topics that are usually explored in caregiver support groups. The PEP intervention group mainly focused on leisure-related support, whereas the IS group

focused on general skills, such as communication skills.[24]

IL-6 levels were measured pre- and post-intervention and one year following the intervention. Results suggested that there was a significant difference observed post-intervention between the PEP and IS group with respect to the change in IL-6 levels. 20.0% of PEP participants noticed a 50% reduction in IL-6 levels compared to only 6.5% of IS participants.[24] However, this change in IL-6 levels from baseline was not significant between the PEP and IS groups at the 1-year follow-up. Also, based on the Reliable Change Index (RCI) cutoffs, 8.6% of PEP participants noticed clinically significant change compared to 0% of the IS participants.[25]

The study also observed the physiological outcomes of the improved IL-6 levels by measuring depression levels in caregivers using the Center for Epidemiological Studies Depression (CESD) scale. Similar to IL-6, the study showed there was a significant difference observed post-intervention between the PEP and IS groups with respect to change in the CESD score. 32.7% of the PEP participants showed a 50% reduction in depression levels compared to only 11.8% of IS participants.[24] Based on the RCI cutoff, 27.9% of PEP participants demonstrated a clinically significant decrease in depression levels compared to only 9.3% of IS participants.[24] However, this change in depression levels was not significantly different between the PEP and IS groups at the 1-year follow-up. A significant difference in negative affect levels was also measured between the groups at the post-intervention measurement, but not at the 1-year follow-up.

The significant reduction in IL-6 levels from pre- to post-intervention suggests that the Pleasant Events Program (PEP) intervention was more successful compared to the active Information-Support (IS) control. The PEP delivers significant physiological changes as seen with the reductions in depression and negative affect levels. Although more research is needed, this study suggests that PEP may help reduce frequent activation of the sympathetic nervous system, which leads to higher IL-6 levels and other physiological symptoms.

PEP also appears more useful compared to other interventions due to its ease in implementation and distribution among dementia caregivers. However, more studies need to be conducted with adaptations to improve PEP efficacy over the long-term before it can be disseminated to caregivers. Future research needs to test PEP interventions that have longer lasting effects and have booster sessions after the intervention is completed. Nevertheless, these preliminary PEP results bring hope of a more convenient way to reduce IL-6 levels and improve physiology of caregivers for patients with dementia.

2.3 A Longer Pleasant Events Program (PEP)

The previous study prompted alterations to the Pleasant Events Program (PEP) intervention by extending the time period to 12 weeks compared to the previous 6-week program. von Kanel et al. (2020) explored the efficacy of the 12-week PEP program in reducing IL-6 levels in caregivers of dementia patients.[26] This study also used the active Information and Support (IS) intervention as the control with the caregiving stress levels measured pre-treatment and IL-6 levels measured pre- and post-treatment.[26] No IL-6 levels were taken at 1-year following the intervention, which were taken in the 6-week program.[26]

Contrary to the previous 6-week study's results, this study did not show any significant time-by-treatment interaction.[26] This suggests that the PEP intervention did not significantly decrease IL-6 levels compared to the IS active control. Additional analysis also suggested that there were no significant time effects, which means that there was no significant reduction in IL-6 levels from pre- to post-intervention for all the participants combined regardless of the treatments.[26] The treatment effect was also not significant, which means that the pre- and post-treatment IL-6 levels in the PEP and IS treatment groups separately were not significantly different.[26]

Although the study did not show PEP to significantly reduce IL-6 levels, indicators of caregiving stress did show significant interactions. There was a higher chance of caregivers showing a significant reduction in IL-6 when they had a higher level of personal mastery, which is having a greater skill set to tackle situations,. With a one-unit increase in personal mastery pre-treatment, there was a 19.6% chance of a decrease in IL-6 levels from pre- to post-treatment.[26] Also, with a one-unit increase in the distress due to caring for a patient's behavioral symptoms, there was a 2.4-fold greater chance of reduction in IL-6 levels.[26] These results align with our understanding since higher personal mastery would allow one to deal with stressful caregiving situations more effectively, and the PEP study would help lower IL-6 levels further. Additionally, those caregivers who care for dementia patients with more frequent and severe behavioral symptoms would have a higher level of stress and would benefit more from the PEP intervention.

As mentioned above, these results are contradictory to those from the 6-week program, which showed a significant reduction in IL-6 levels in the PEP group compared to the IS group. This can be attributed to several differences between the 6-week and 12-week study. One difference is the treatment duration: the results suggest that the shorter intervention is more effective. This may be because longer interventions are more burdensome on the participants.[27] The longer intervention may also lead to a decrease in overall interest and morale of the participants, which may have some physiological effects. Additionally, the results suggest that PEP may be helpful for caregivers with higher personal mastery levels and those caring for dementia patients with higher severity and frequency of behavioral symptoms.

2.4 Summary

Higher IL-6 levels have been linked to increased severity of illnesses, like pneumonia, and higher mortality rates due to its association with increased risk of cardiovascular and cerebrovascular incidents.[28] Dementia caregivers tend to have a significantly higher IL-6 level compared to non-caregivers, exposing them to these higher risks. Therefore, it is crucial to establish a psychoeducational intervention that helps caregivers of dementia patients to reduce their IL-6 levels.

The studies reviewed above provide promising results. Mausbach et al. (2011) suggested that IL-6 levels were significantly associated with stress when coping self-efficacy (CSE) levels of dementia caregivers were low.[22] However, IL-6 was not associated with stress when CSE levels were high, which means that coping self-efficacy practices allow caregivers to have lower IL-6 levels despite the caregiving stress. Future studies are still needed to explore whether coping self-efficacy (CSE) interventions reduce IL-6 levels from pre- to post-intervention.

The Pleasant Events Program (PEP) studies discussed above also show promising results. PEP aims to help caregivers for dementia patients increase their ability to participate in leisure activities and pursue their interests despite their caregiving responsibilities. The 6-week study showed that PEP was successful with significant reductions in IL-6 levels from pre- to post-intervention. The shorter PEP also showed positive physiological results as it showed significant reductions in depression and negative affect. However, the 12-week PEP study did not show significant reductions in IL-6 levels from pre- to post-intervention, which may suggest that longer interventions may have reduced effectiveness.

Psychoeducational interventions may help caregivers for dementia patients by reducing the frequency of activation of their sympathetic nervous system caused by stress, thereby reducing IL-6 levels. However, more research, with different types of intervention delivery methods and structures, needs to be performed before marketing these interventions to caregivers for dementia patients. For example, more frequent intervention sessions in

a shorter period may potentially yield better results for caregivers.

Conclusion

The research studies discussed over the course of this paper have provided key highlights on the association between IL-6 levels and caregiving activities for people living with dementia. Caregivers are known to face a higher level of daily stress and burden due to their increased responsibilities and costs. The 6-year longitudinal study discussed earlier showed that IL-6 levels in caregivers were predicted to increase at a rate approximately 4 times faster than in non-caregivers.[17] Kiecolt-Glaser et al. (2003) also showed that there were no significant differences in IL-6 levels between current and former caregivers, which suggests that the physiological effects of the caregiving and increased stress may be more long-term in nature.[17]

This association between IL-6 levels and caregiving can be explained by the idea that the stress from caregiving overstimulates the proinflammatory response and leads to higher IL-6 levels. Additionally, these effects are more long-term potentially due to the stress having a more permanent effect by prolonging the proinflammatory response and keeping the IL-6 production levels elevated.

Higher IL-6 levels over an extended period of time can have several physiological consequences. For example, it can affect the anticoagulant and profibrinolytic capabilities of endothelial cells. This leads to a higher risk of blood clots and hence cardio-cerebrovascular diseases, such as heart failure, myocardial infarction, ischemic stroke, and atherosclerosis.[5] Due to these risk factors, it is crucial that the caregivers for PLWD receive an intervention to reduce their IL-6 levels.

Moving forward, more research is needed to help develop interventions to reduce IL-6 levels in caregivers. Psychoeducation interventions with different delivery methods, such as virtual training, online modules, and in-person sessions, along with different time frames, such as a 1-month versus 6-month training, need to be tested to create the most effective intervention. Additionally, mindfulness and meditation interventions, and physical activity interventions, such as yoga, need to be studied as potential methods to reduce IL-6 levels in caregivers.

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