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What is the Personal Immune Price for Hospice Caregivers? A Case-Control Study

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Introduction

In 2016, more than 1.43 million patients received hospice care in the United States and nearly half of the hospice days of care were provided at private residences [1]. Home-based hospice care increases the likelihood of death at home by 7 to 8 fold [2]. Although spousal caregivers experiencing strain were shown to be 63% more likely to die within 4 years than non-caregivers, these findings were not replicated in population based studies involving different caregivers [3-6]. Caregivers of terminal cancer and hospice patients often face increased psychosocial stressors and a perception of crisis specially when a loved one's symptoms continue to intensify near the end of life [7]. In a study involving caregivers of Alzheimer and other dementia patients, 72% acknowledged they felt a sense of relief after the patient's death [8].

Stress ensues when events or environmental demands exceed an individual's perceived ability to cope. Stress modulates health changes by a complex interplay of neuroendocrine and immune system changes [9]. Daily stressors faced by caregivers of dementia patients are known to cause higher levels of serum inflammatory biomarkers, including cytokines, C-reactive Protein (CRP) and activation of the coagulation system, which can have adverse cardiovascular implications and accelerated frailty syndrome in caregivers [10-13]. Long-term caregivers for dementia patients show suboptimal antibody production in response to influenza, tetanus, and pneumococcal vaccinations [14-16]. Additionally, caregivers who feel chronic caregiver burden show decreased Natural Killer (NK)-cell responses and reduced T-cell proliferation in response to stimulation [17,18]. Caregiving is known to influence the percentages of peripheral blood lymphocytes, including T cells, B cells, and NK cells [9,15,16].

Hospice caregivers are in a unique position, as the majority of patients continue to reside at home, and approximately 40.5% hospice patients die within 14 days of enrollment [1]. Though most of the medical literature regarding stress-induced immune changes comes from caregivers of patients with Alzheimer disease and dementia, dementia comprised only 18% of hospice admission in the United States in 2016 [1]. Hospice informal caregivers deserves study to confirm or negate immune dysregulation as reported in dementia patient caregivers. To our knowledge this is the first investigation into different inflammatory biomarkers as mediators of immune related changes in hospice informal caregivers.

Methods

All procedures for recruitment and testing were approved by the Mayo Clinic Institutional Review Board prior to study initiation. Blood from Biobank [19]. Volunteers and current hospice caregivers was collected into vacutainer tubes containing sodium heparin. Blood tubes were spun and plasma collected, aliquoted, and frozen at -80°C. Peripheral Blood Mononuclear Cells (PBMCs) were isolated by Ficoll Paque (Sigma-Aldrich, Inc.) gradient. After isolation, cells were washed in 1×phosphate buffered saline (Human cytokine/chemokine panel 1) PBS, viably frozen, and stored in liquid nitrogen until analysis. Plasma cytokine levels and PBMC frequencies were determined as previously described [20].

Briefly, cytokine concentrations were determined using cytokine multi-plex kits as per manufacturer instructions

(Millipore Sigma). Protein concentrations were calculated using a standard curve with a dynamic range of 1.6 to 5,000 pg/mL using MILLIPLEX Analyst software (Millipore Sigma). Multiparametric flow cytometry was utilized to ascertain PBMC subset frequency. Cellular subsets enumerated included T, B, NK, myeloid, and dendritic cells. Samples were analyzed by flow cytometry on the Guava Easycyte 8HT and data analysis was performed with Guava Soft software, version 3.1.1 (Millipore Sigma).

Caregivers

Family caregivers who had been providing care for at least 2 weeks from initiation of hospice care and met the inclusion and exclusion criteria listed below were contacted via telephone by a coinvestigator (A.L.) for recruitment after their electronic medical record had been reviewed (for authorization for research). Home hospice case managers and social workers also distributed fliers; so interested caregivers could directly contact the coinvestigator in charge of recruitment for screening by telephone. Participants were mailed a written informed consent form to sign prior to data collection, as well as a questionnaire about their general health, medications and physical activity. After completion of the written consent form and questionnaire, they were scheduled for a 1-time blood draw. All participants received a $20 gift certificate to a local grocery or department store as remuneration.

Inclusion and Exclusion Criteria

To be included, participants had to be primary, unpaid caregivers living with a hospice patient with responsibility for a minimum of 8 hours each day, at least 18 years of age, and able to provide informed consent. Caregivers were excluded if they had any active malignancy, autoimmune disease, infection, coronary artery disease, severe renal failure requiring hemodialysis, or severe hepatic dysfunction. If the caregiver did not provide permission or access for research to their medical record, they were also ineligible.

Control Group

Self-reported, healthy, age- and sex-matched individuals from the Mayo Clinic Biobank were chosen as controls. Details regarding the Biobank resource and enrollment procedures have been described elsewhere [19]. All control subjects were patients of Mayo Clinic with Electronic Medical Records available to verify eligibility. Blood was scheduled to be drawn between 6:00 AM and 10:00 AM to reduce diurnal variation and from February through May to avoid seasonal effects.

Statistical Analyses

Categorical variables were summarized as frequency (%) and continuous variables as median (interquartile range). We used paired *t* tests to compare biomarker values in family caregivers to matched controls. To correct for the existence of right-skewed data, analyses were performed using van der Waerden test (ie, normal score) transformed biomarker values. All statistical tests were 2-sided, and all analyses were carried out using SAS software (SAS Institute, Inc.).

Results

A total of 39 caregivers were included in the study after providing informed consent. Demographic data was available for 37 patients and blood samples were available from 39 patients. (Tables 1,2) show demographics and characteristics of caregivers respectively. Most of the caregiver were providing >10 hours of daily care and one third were taking care of patients for more than 2 years. Median duration of care provided by family members was 6 months. Hospice qualifying diagnosis for care recipients included advanced cancer (54.05%), heart failure (10.81%), dementia (8.1%), frailty (8.1%), COPD (5.4%) and others (13.5%). 35.1% were taking aspirin and statin medications. 32.4% reported prior smoking and 5.4% reported active smoking. Blood samples from 39 caregivers were compared with age and sex matched controls (Tables 3,4).

Variables	N=37, Frequency (%)
Sex	
Female	33 (89.2)
Male	4 (10.8)
Age, y, mean (range)	69.7 (45-88)
Marital status	
Married	34 (91.9)
Single	2 (5.4)
Widowed	1 (2.7)
Annual household income	
<$25K	2 (5.4)
$25-50K	17 (45.9)
$50-75K	8 (21.6)
$75-100K	4 (10.8)
>$100K	3 (8.1)
Unknown	3 (8.1)
Employment	
Full-time	5 (13.5)
Part-time	6 (16.2)
Not working	4 (10.8)
Retired	21 (56.8)
Unknown	1 (2.7)

Table 1. Caregivers Demographics.

Variables	N=37, Frequency (%)
Hours per day spent as caregiver	
0-10	16 (43.2)
>10	21 (56.8)
Total duration of caregiving in months	
<1	12 (32.4)
1-12	9 (24.3)
12-24	3 (8.1)
>24	13 (35.1)
Relationship to patient	
Spouse	33 (89.2)
Child	2 (5.4)
Parent	2 (5.4)
Medical Problems	
Hypertension	16 (56.7)
Cardiac	3 (8.1)
Diabetes Mellitus	5 (13.8)
Pulmonary disease	2 (5.56)
Sleep disorder	3 (8.1)
History of cancer	9 (18.4)
Gastrointestinal disorder	7(19.4)
Mood disorder	7(19.4)

Table 2: Caregiver characteristics.

We found significant differences in cytokines and chemokines between caregivers and age- and sex-matched controls, as delineated in (Tables 3,4), respectively.

Biomarkers	Pairs	Caregiver, Median	Control, Median	Paired Difference, Median (IQR)	P Value
IL-2	38	3.2	1.9	0.3 (−1.1, 5.8)	0.01
IL-4	38	2.1	8.4	−1.3 (−23.3, 0.3)	<.001
IL-6	38	2.3	2.1	0.1 (−1.6, 1.5)	0.24
IL-8	38	4.2	1.6	1.4 (−0.4, 4.8)	0.005
IL-13	38	2.5	2.5	0.1 (−3.5, 2.1)	0.05
IL-12	38	12.2	7.7	5.5 (−0.6, 17.4)	0.003
IL-1α	38	6.2	3.9	−1.1 (−2.2, 15.2)	0.65
IL-1β	38	2.8	1.6	1.1 (−0.7, 6.1)	0.001

IFNγ	38	10.3	14.1	−1.8 (−10.0, 7.0)	0.33
TGFα	38	2.8	2.7	−0.2 (−0.9, 1.9)	0.54
TNFα	38	9.6	10	1.1 (−5.0, 4.2)	0.88
TNFβ	38	4.1	3.2	−0.9 (−2.7, 7.4)	0.21
CRP	38	2.3	0.9	1.2 (−0.1, 4.3)	<.001
CD3+CD8+	35	18.5	10.6	8.0 (−0.2, 15.6)	0.003
CD3+CD4+	35	35	25.9	9.1 (−1.1, 18.5)	0.001
CD16+56+	38	11.3	7.2	5.5 (−1.6, 10.6)	0.003
CD3+69+	39	5.4	2	3.4 (1.0, 6.5)	<.001
CD3+62L+	39	19	5.9	11.9 (6.4, 21.5)	<.001
CD4+TIM3+	39	4.1	1	3.1 (0.6, 4.5)	<.001
Treg	39	64.9	57	6.3 (−1.7, 15.3)	0.005
G-CSF	38	75.8	134.6	−59.3 (−107.3, 1.3)	<.001
GM-CSF	38	21.7	7.5	8.4 (−5.1, 29.9)	<.001
EGF	38	61	13.8	49.9 (5.5, 93.4)	<.001

Abbreviations:

CRP : C-Reactive Protein

EGF : Epidermal Growth Factor

G-CSF : Granulocyte–Colony-Stimulating Factor

GM-CSF : Granulocyte Macrophage–Colony-Stimulating Factor

IFN : Interferon

IL : Interleukin

IQR : Interquartile Ranges

TGF : Transforming Growth Factor

TNF : Tumor Necrosis Factor

Treg : Regulatory T Cell

Table 3: Cytokines.

Biomarkers	Pairs	Caregiver, Median	Control, Median	Paired Difference Median (IQR)	P Value
Eotaxin (CCL11, CCL24, CCL26)	38	95.3	241.7	−148.3 (−246.3, −94.5)	<.001
Fractalkine (CX3CL1)	38	93.4	127.4	−32.6 (−85.3, 13.0)	0.009
GRO (CXCL1, CXCL2, CXCL3)	37	356.7	239	127.7 (−73.0, 339.1)	0.007
IP10 (CXCL10)	38	335.8	1506.5	−1,092 (−2,211, −538.8)	<.001
MCP-3 (CCL7)	38	17	159.6	−144.2 (−151.7, −132.5)	<.001

MDC (CCL22)	38	784.8	1434	−698.4 (−1051, −355.0)	<.001
MIP1b (CCL4)	38	20.8	37.6	−14.5 (−32.9, 2.6)	<.001
MCP-1 (CCL2)	38	241	199.8	−0.8 (−75.6, 190.4)	0.351

Abbreviations:

GRO : Growth-regulated oncogene;

IP : Induced protein;

IQR : Interquartile range;

MCP : Monocyte chemotactic protein;

MDC : Macrophage-derived chemokine;

MIP : Macrophage inflammatory protein;

Table 4: Chemokines.

Discussion

Majority of the family caregivers in our study were elder, retired and female spouses of patients enrolled in hospice. As patients get weaker with advance illnesses and transition to hospice, they experience rapid decline, which predisposes caregivers to various stressors. Various Psychosocial and environmental stimuli experienced by caregivers result in activation of neuro-hormonal system and lead to immunological changes. Results from this study provide a snap shot of immune changes in family caregivers of hospice patients. These changes may be a part of biological coping mechanism but can also result in deleterious health outcomes. Our results showed increased IL-2 and IL-12, but reduced IL-4 levels in hospice caregivers, which indicate increased cell-mediated inflammatory response. Although findings have been variable in dementia caregivers, we found higher percentages of peripheral CD4+ lymphocytes, CD8+ lymphocytes, and CD56+16+Natrual killer cells in hospice caregivers. We also found higher expression of CD62L in caregivers indicating increased trafficking of naïve lymphocytes into lymph nodes where they become activated [21]. These results imply increased inflammatory changes in hospice caregivers compared to the age- and sex-matched control group.

(Table 3) shows that a pro-inflammatory cytokine IL-8, also known as chemokine CXCL8, was higher in caregivers than controls, consistent with higher inflammatory changes in caregivers. Another inflammatory cytokine, IL-1β, was elevated in caregivers; it is secreted in an active form by a variety of cells, mainly monocytes and macrophages. Similar to IL-8, IL-1β mediates recruitment of neutrophils and plays vital role in inducing inflammation [22-23].

Chemokines are strongly associated with immunity and inflammation. There are different chemokine families, including CC, CXC, CX3C, and C-chemokines. Their basic role is to help immune cells navigate and orchestrate an immune response. We found elevated levels of important chemokines as well (Table 4). We observed lower levels of CXCL10, an important chemokine with tumor-suppressive activities. CXCL10 has been inversely correlated with tumor-related growth. In colorectal and ovarian cancers, lower levels of CXCL10 have been suggested as a poor prognostic marker [24,25]. Caregivers also had higher expression of TIM-3, which has also been associated with T cell exhaustion and predisposition to various malignancies [26]. Eotaxins, which are important chemoattractant for eosinophils and have been associated with allergic diseases, were lower in caregivers. This can be explained by possibility of a reflex inhibitory feedback or protective pathway to limit increased inflammation.

CD69 is another important inflammatory marker, which was higher in caregivers. Increased expression of CD69 and IL-1β have been associated with atherosclerosis [27], we also found higher levels of CRP in caregivers, which not only indicates inflammation occurring at the endothelial level during atherosclerosis but it is also associated with future cardiovascular events. CRP has been considered as a true risk factor and mortality predictor for cardiovascular disease. Chronic caregiving for Alzheimer disease and dementia patients has been shown to be associated with compromised cardiovascular health, high Framingham risk scores, and an increased burden of atherosclerosis [28,29]. A study including caregivers of cancer patients showed increase in CRP over period of time [12]. Our findings of increased CRP, CD69 and IL-1β along with higher prevalence of hypertension in caregivers suggest that hospice caregivers may have higher risk of atherosclerotic heart disease.

Various researchers [9,30,31], have suggested that the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system provide activation of stress-related immune dysregulation.

We did not assess levels of catecholamine, pituitary hormones, or cortisol in our participants. Caregivers were requested to provide blood sample between 6 AM and 10 AM to match time with control participants but we were not able to assess compliance with this request. Other limitations of include, small sample size, cross sectional nature and convenient sampling method. We were also not able to control for smoking status and medication used by caregiver.

In this study we have identified that elder female spouses of hospice patients with advanced diseases have association with increased inflammatory markers, higher risk for malignancy and cardiovascular diseases. This group of caregivers may need additional resources and monitoring so potential risks associated with inflammatory changes can be abated by timely intervention. Currently hospice model include grief counseling for family members of patients, our data provide support for broadening this service to include education on health maintenance and partnership with primary provider of caregivers to optimize age appropriate cancer screening and counseling to reduce risk for cardiovascular disease.

Conflict of Interest and Financial Disclosure:

None.

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