Immune Relevant Behavioural Interventions: Immunological Evidence as an Integral Measure of Behavioural Interventions for Rheumatic Diseases, a Review of Current Research

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INTRODUCTION

Behavioural interventions and immunologic indicators of health, disease activity, and immune function are discrete subject areas, which have been thoroughly explored in academic research. While many research studies have looked at these subject areas individually, there is less empiric exploration into the relationship between them within rheumatology.[1-4] This is particularly relevant for disorders of the immune system, such as autoimmune diseases, where these subject areas are inextricably related.

Autoimmune disorders have well-established pharmacotherapies and treatment regimens, which address prolonged life, reduce disability, and improve quality of life.[5] However, effective treatment for disorders of the immune system necessitate a multimodal approach that addresses patient-level factors and disease self-management.[6] Behavioural interventions often set out to change these factors in an individual or group as it relates to their physical health. Common elements of behavioural interventions include education, which can be structured or unstructured; experiential learning; and the application of skills learned.[7] In addition to

physical health, behavioural interventions have been employed to reduce the negative effects of adverse psychological states, such as anxiety or depression, by teaching and applying coping skills.[8] The link between the immune system and emotion has been well studied; however, the mechanism of action is complicated, likely due to this complex relationship and variance between psychological states.[9-11]

Other patient-level factors observed to be associated with altered immune function are socioeconomic status, race, gender, and employment.[12-15] Even though these patient-level factors are difficult to directly modify, they are crucial for understanding the connection between overall health and immune function. This is due to the relationship between the individual and their immune system being bidirectional.[16] Not only does an individual's physical health, emotional health, and behaviour affect their immune system, but immune system modulation can lead to changes in emotional well-being and cognition.[11] Given the link between the immune system and patient factors established in research literature, the authors conducted a limited review to provide evidence for the utility of measures of immune function in the assessment of behavioural interventions for rheumatic diseases.

IMMUNE FUNCTION

Many psychological states and environmental factors have connections with the function of an individual's immune system. This is exemplified in the effect that stress can have on the immune system. Psychological stress can shift the Type 1/Type 2 cytokine balance towards Type 2 and result in immune dysregulation. This process is mediated through decreased peripheral blood mononuclear cell interferon-γ and increased IL-10, resulting in reduced host defenses to harmful pathogens.[17] Allostatic load is the deterioration of the body and brain from chronic overactivity or inactivity of physiological systems that aid with adaptations to environmental challenges.[18] Long-term exposure to stressors can lead to a build-up of the physiologic changes that diminish immune response. This wear and tear over time further diminishes the body's ability to fight off infection, and can lead to other risk factors, including obesity, cardiovascular damage, and atrophy of nerve cells in the brain.[19]

Furthermore, the role of cytokines and the immune system may be greater. According to the cytokine hypothesis of depression, pro-inflammatory cytokines may act as neuromodulators and play a critical role in the modulation of depressive disorders. Supporting evidence for this theory includes the correlation between inflammatory autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), with depressive symptomatology. Moreover, therapies involving the provision of pro-inflammatory cytokines induce depressive symptoms in some patients. Similar outcomes have also been observed in animal models.[20] While these examples would indicate that the relationship between cytokines and depression is unidirectional, a bidirectional relationship, and the third variable problem have not been ruled out. In addition to depression, a similar relationship has been observed between immune dysfunction and anxiety. This effect is posited to be a result of oxidative stress to immune cells and tissues, which mimics the effects of ageing.[15,21]

The function of the immune system has also been shown to be linked to social support and mental and physical discomfort. Perceived social support is correlated with a greater number of natural killer (NK) cells in the blood. NK cells are cells that combat and kill pathogens in the host.[22] Therefore, individuals with a greater number of NK cells have greater innate immunity and ability to fight off infections.[23] On the other hand, exposure to distressing environments can have a negative effect on the immune system. The perception of pain and the immune system are also linked, such that the perception of pain activates immune cells to mobilise a response to the perceived threat.[24] Pain can subsequently compound the allostatic load that damages the host's immune system over time through the induction of stress and anxiety. This relationship between pain, inflammatory mediators, and associated psychological effects suggests an environment where positive feedback is not only possible, but probable. As a result, behavioural interventions could be directed at any one of these factors with the intent of improving the immune system.

BEHAVIOURAL INTERVENTIONS AND IMMUNE FUNCTION

Behavioural interventions have attempted to address the psychological manifestations and pain that influence this feedback loop. Despite the known relationship between the immune system and modifiable patient factors, measures of the immune system are not prevalent in the domains of rheumatology research. Much of the previous research lies in the study of cancer. For example, McGregor et al.[25] examined the effect of a cognitive-behavioural stress management (CBSM) intervention on females with breast cancer. Outcomes of interest included immune function, emotional well-being, and perceived benefit from the intervention. Females in the CBSM programme perceived greater benefit than those in the comparison group. In addition, at a 3-month follow-up visit, the CBSM group's immune systems had shown greater lymphocyte proliferation. This result was positively correlated with a participant's self-reported benefit from the programme. Similarly, a review conducted by Leucken and Compas[26] argued that there is a wealth of evidence to indicate that behavioural interventions improve emotional and physical factors in patients with cancer, which in turn confer benefit to the immune system by lowering cortisol levels and improving the number of naturally circulating NK cells. Notably though, they were unable to establish a relationship between these variables and improved outcomes, such as life-expectancy.

More recently, a meta-analysis of 76 randomised controlled studies of behavioural interventions in cancer assessed a broad range of immunologic effects. Results were modest but generally positive for the immunologic outcomes assessed. Key conclusions included improving methodological rigor in such trials in order to fully cognise potential intervention benefits.[27] Furthermore, these findings suggested the importance of including disease-specific immune response measures to identify the modifications that may influence disease activity and outcomes. Another meta-analysis conducted in HIV/AIDs was similarly positive. Fifteen controlled trials were included in the analysis, which concluded that behavioural interventions in this population were effective in improving symptoms of stress, depression, anxiety, and anger. However, the connection to immunologic improvements, as measured by cluster of differentitation 4 cell counts, was more modest. Further research into the complex relationship between the immune system and behavioural health was recommended.[28]

Such results are not limited to disease-bearing populations. Caregivers of individuals with dementia who took part in a five-session structured support group experienced improvement in many psychosocial domains, including depression scores, anxiety, and anger. Statistically significant improvements in NK cell activity were also observed.[29] Though some relationships need further exploration, the link between psychosocial well-being and the immune system is generally robust.[30] These examples provide a basis for further exploration of the immune system as an outcome of interest in behavioural interventions. If positive outcomes are achieved, the implementation of such multimodal examinations will provide a biological basis for the benefits conferred by behavioural interventions. Moreover, with improved methodological rigor, such as including larger sample sizes, randomised controlled designs, and further exploration in diverse disease types, a causal relationship may be established between perceived psychosocial well-being and immune function.

RESEARCH METHODS FOR ASSESSING IMMUNE FUNCTION

Autoimmune diseases are one such subset of conditions where the underlying pathogenesis warrants a tailored approach to assessing changes in immune function. In the case of SLE and rheumatoid arthritis, disease pathogenesis is regulated largely by T cells. Downregulation of regulatory T cells and an increase in the number of effector T cells leads to the characteristic symptoms of inflammation, tissue damage, and autoantibody production.[31,32] T cells may be the most relevant immunologic outcome measure for behavioural interventions in autoimmune disease as it plays the greatest role in modifying disease characteristics. One study has explored this in SLE and found positive relationships between decreases in patient-reported depression and anxiety and T helper Type 1/T helper Type 2 cytokine balance following a 12-week behavioural intervention.[33] Future investigations may benefit

from exploiting these same methods in a larger sample size with a randomised controlled design to indicate causality.

CONCLUSION

Immune function is closely linked with other aspects of human health, whether directly through an immune response to a pathogen, or indirectly in the cases of cortisol/allostatic load and autoimmune disease. However, these relationships have been understudied in the domain of behavioural interventions. Behavioural intervention is a broad term with many applications towards different diseases and conditions, but most notable for negative psychological states. With the potential positive impact behavioural interventions can bring upon this domain of health, it is of paramount importance that appropriate measures of intervention success are employed. For this reason, as well as the connection between the immune system and psychological health, there is an imperative for measures of immune function to be increasingly implemented in gauging the success or failure of these programmes. Aside from the previously outlined associations and ability to detect meaningful physiological changes, these measures may provide additional benefits to researchers.

First, as previously discussed, there are several types of measures that can be employed for various study designs or variables of interest, giving this form of data a wide range of applications. Second, previous studies indicate that they are reliable and able to provide consistent measurements, which can be correlated with other data, used as a controlling variable, or used as primary/secondary outcome variable.[34,35] Where they are not as reliable, they are convenient; for example, with salivary cortisol. Collecting and analysing samples is simple (mouth swab) and does not require extensive lab equipment. However, this method is subject to notable variation depending on the time samples are collected and whether the subject has recently consumed a beverage.[35]

Nevertheless, other measures of immune function can be made easier to analyse through collaboration for a holistic approach to disease modification. There is evidence to suggest that frozen blood samples can be assessed for cytokines and other markers of immune activity with similar variation as compared to fresh samples.[33] If gathering this type of data is not feasible for a localised research team, collaboration with a facility or research partner with the ability is a plausible option. Finally, many behavioural interventions include patient-reported outcomes as a primary variable of interest. In the context of trying to change an individual's behaviour, gathering patient perception and attitude is central to the success therein. However, there is noteworthy bias inherent to this model. A subject who has undergone an intensive behaviour modifying intervention is likely to report reduced stress due to the placebo effect as well as personal bias from having been a participant. For this reason, introducing an immunologic indicator of emotional well-being would help to remove this bias by showing the physiological effects of the intervention in concert with the patient-reported outcomes.

Overall, the association between immunologic function and various factors that behavioural interventions can influence is robust but not entirely complete. Therefore, it is important that researchers include these measures as an integral part of rheumatic research initiatives to close gaps in knowledge and show the biologic basis for interventions seeking to modify autoimmune disease pathogenesis through behaviour change.

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