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Review Article

Psychological manifestations in patients with tuberculosis: prevalence and contributing factors

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ABSTRACT

Tuberculosis (TB) continues to be a major global health concern impacting millions of people each year. Beyond its outward symptoms TB can have a significant negative influence on psychological health and cause psychological anguish in those who are afflicted. The purpose of this review is to recapitulate the frequency and contributing variables of psychological discomfort in TB patients. Previous studies show varying prevalence rates of psychological distress which frequently manifests as stress, worry, and depression. Numerous factors such as sociodemographic characteristics the severity of the disease the treatment plan, stigma, and social support. these factors can alter gene expression patterns, epigenetic modifications, and immune responses linked to higher psychological distress. Psychological factors like stress, anxiety, and depression can influence gene metabolism in TB patients through various mechanisms. These factors impacting TB susceptibility, disease progression, and treatment outcomes. To effectively address the mental health needs of TB patients, it is imperative to comprehend the prevalence and factors of psychological distress in tb population. Promote the holistic well-being of TB patients, it is imperative that mental health treatments be integrated into TB care in conjunction with initiatives to lessen stigma and enhance social support.

1. Introduction

Tuberculosis (TB) Caused by Mycobacterium tuberculosis (MTB) continues to pose a significant global health challenge, stemming from its ancient origins and enduring impact on health.[1] TB primarily affects the lungs and presents with symptoms such as cough, fever, and fatigue. Despite advancements in TB management the disease remains a major public health concern with millions of new infections and deaths annually.[2] The bacterium that causes TB, MTB replicates about 50 times more slowly than other bacterial pathogens because of this TB illness progresses more slowly than well-known viral epidemics like coronavirus 2 or Ebola.[3] The COVID-19 pandemic has further complicated TB control efforts decline in reported cases and potentially impeding progress towards elimination goals.[4] TB treatment involves prolonged drug regimens, impacting patient's physical and psychological well-being.[5] According to 2017 research World Health Organization (WHO) Over 300 million people worldwide spanning all age categories suffer from depression.[6] Psychological distress, including depression and anxiety is prevalent among TB patients influenced by factors such as poverty, chronic illness, and treatment side effects. This distress not only affects treatment adherence but also exacerbates adverse outcomes and transmission.[7] Despite its significance psychological health receives inadequate

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attention in TB programs.[8] Depression commonly coexists with TB increased morbidity and mortality. Previous studies indicate that the prevalence of depression among TB patients varies widely ranging from 9.93% to 47.2%. This disparity can be attributed to differences in assessment tools. The comorbidity of depression and TB exacerbates both conditions resulting in poor treatment adherence and progression to multidrug-resistant tuberculosis (MDR-TB), and increased mortality.[9] A systematic review and meta-analysis revealed that before starting the treatment of TB approximately 50% of MDR-TB patients experience depression, with anxiety and psychosis. This highlights the need for comprehensive mental health screening and interventions in TB care to improve patient outcomes and quality of life.[10] In this review we highlighting the significant impact of psychological distress on individuals particularly those with TB marked by symptoms of depression and anxiety. Psychological distress stands as a prominent contributor to the global burden of disease often coexisting with other medical conditions and adverse health outcomes including treatment nonadherence and risky behaviors. Evidence indicates a high prevalence of psychological distress among TB patients in developing countries, surpassing rates in the general population.[11] Various factors including social, medical, and individual behavioural aspects contribute to psychological distress among TB patients such as poverty, TB-HIV coinfection, and drug-related reactions.[12] Despite its substantial effect on TB patient's overall health and treatment outcomes, research in low- and middle-income countries, remains limited.[13] Understanding the scope and associated factors of psychological distress among TB patients is critical for elucidating TB impact on psychological well-being and planning effective interventions to enhance treatment success rates.[14] Early detection and appropriate interventions show promise in addressing psychological distress and improving TB outcomes. However, research in this area remains limited.[8]

2. Psychological Factors in TB

Individuals with TB often grapple with anxiety and depression, which can be triggered by the diagnosis and the prospect of enduring prolonged treatment. Anxiety may arise from concerns about treatment effectiveness, medication side effects, fear of transmission, and uncertainty about the future. Depression is a widespread mental health issue in modern society affecting around 4.4% of the global population. The South-East Asia region accounts for a significant portion, with 20% of worldwide cases attributed to it, and India alone sees approximately 18% of global occurrences. In India, around 15% of the population is estimated to suffer from depression. In severe cases depression can culminate in suicidal ideation and a diminished quality of life.[15] Depression can stem from disruptions to daily life, social isolation, disease stigma, and TB symptoms. Both conditions significantly impact patient's well-being treatment adherence and overall quality of life. Coping mechanisms are pivotal in managing psychological distress among TB patients. Positive strategies such as seeking social support maintaining a healthy lifestyle, practicing relaxation techniques, and adhering to treatment can alleviate anxiety and depression symptoms. Psychotherapy and counselling also offer valuable tools for addressing negative emotions and fostering effective coping strategies. A list of research on the relationship between psychological factors and TB are depicted in Table 1.

3. Stigma and Social Perception

Historical and contemporary perspectives on TB-related stigma have evolved over time shaping perceptions of the disease and its impact on patients and communities. In the past, TB was often associated with social stigma, fear, and ostracization due to misconceptions about it's transmission and perceived link to poverty, immorality, and uncleanliness.[16] Patients with TB were often marginalized, isolated, and discriminated against foremost to social exclusion and negative stereotypes.[17] During the 19th and early 20th centuries, sanatoriums were established to isolate TB patients from the general population. While these institutions aimed to prevent disease transmission, they also reinforced stigma by segregating patients and perpetuating the idea that TB was a moral failing rather than a medical condition. Stigmatizing policies, such as mandatory isolation, quarantine, and forced sterilization of TB patients, were implemented in some regions, exacerbating social stigma and discrimination against individuals with TB.[17] With medical advancements, such as antibiotics and improved public health measures, TB is now better understood as a treatable and preventable disease. Still, stigma persists due to lingering misconceptions, fear of transmission, and cultural beliefs about TB. TB-related stigma continues to impact patients and communities discrimination, social exclusion, and psychological distress. Patients may experience shame, guilt, and fear of disclosure, hindering their access to care and treatment adherence.

4. Treatment Adherence and Barriers

Treatment adherence is crucial for successful TB management but various challenges can hinder medication adherence including financial constraints and mental health comorbidities. TB treatment typically involves a combination of multiple antibiotics taken over a prolonged period, ranging from six months to over a year. The complexity and duration of treatment regimens can pose challenges for adherence as patients may struggle to adhere to daily medication schedules. Some TB medications

can cause adverse side effects such as nausea, vomiting, and hepatotoxicity. Patients may discontinue treatment or skip doses to alleviate discomfort from side effects leading to treatment failure and drug resistance.[5] TB-related stigma and discrimination can deter patients from seeking care or adhering to treatment due to fear of social judgment, isolation, or loss of employment. Weak health systems, lack of access to healthcare facilities, and inadequate patient education and support can contribute to poor medication adherence among TB patients. TB treatment may incur financial costs for patients, particularly in settings where medications are not provided free of charge. High out-of-pocket expenses for medication and healthcare services can present barriers to treatment adherence, especially for individuals from low-income households. TB patients may experience loss of income and productivity due to illness, hospitalization, or isolation, further exacerbating financial strain and limiting their ability to afford medication and healthcare expenses. Mental health issues can negatively affect treatment adherence and overall well-being. Addressing mental health comorbidities requires integrated care approaches that combine TB treatment with mental health services, counselling, and psychosocial support. Collaborative care models involving multidisciplinary teams of healthcare professionals can help identify and address mental health needs alongside TB treatment. Medication adherence challenges, financial constraints, and mental health comorbidities are significant barriers to effective TB management. Addressing these barriers requires comprehensive strategies that address social determinants of health strengthen health systems provide financial support and integrate mental health services into TB care.[17] By addressing these challenges, we can improve treatment adherence, reduce disease burden and enhance outcomes for TB patients.

5. Gene Metabolism in TB

5.1. Immune system genes

Genetic disparities play a substantial role in determining a person's susceptibility to TB infection and the subsequent immune response. The genetic basis of TB susceptibility and immune response variability can provide insights into disease pathogenesis, inform risk stratification strategies and guide the development of novel interventions such as vaccines and immunomodulatory therapies aimed at preventing TB infection and improving treatment outcomes. Also genetic testing may help identify individuals at increased risk of TB and guide personalized approaches to TB prevention and treatment.

5.1.1. Human leukocyte antigen (HLA) genes

HLA genes, particularly those within the major histocompatibility complex (MHC) region, show a vital role in presenting antigens to T cells and initiating the adaptive immune response. Certain HLA alleles have been associated with increased susceptibility to TB infection or progression to active disease, while others are linked to protection. For example, variants in the HLA-DR and HLA-DQ genes have been implicated in TB susceptibility and severity.

5.2. Interferon-gamma (IFNG) pathway genes

Interferon-gamma (IFN-γ) is a key cytokine involved in the immune response to TB infection, particularly in activating macrophages to kill intracellular bacteria. Genetic variations in genes encoding components of the IFN-γ pathway, such as IFNG, IFNGR1, and IFNGR2, can influence susceptibility to TB and the ability to mount an effective immune response. Polymorphisms in these genes have been associated with increased risk of TB infection and progression to active disease.

5.2.1. Toll-like receptor (TLR) genes

Toll-like receptors are pattern recognition receptors that play a crucial role in recognizing microbial pathogens including TB. Genetic variations in TLR genes, such as TLR2 and TLR4, can affect innate immune responses to TB infection. Variants in these genes have been linked to altered cytokine production, impaired bacterial recognition, and increased susceptibility to TB.

5.2.2. Cytokine genes

Cytokines are key regulators of the immune response and play a central role in TB pathogenesis. Genetic differences in the genes that encode the inflammatory cytokine IL-1 can affect the development and susceptibility to tuberculosis. Polymorphisms in these genes have been associated with altered cytokine production, inflammation, and TB outcomes.[6,18]

5.3. Neurotransmitter genes

The role of neurotransmitter pathways in regulating mood and emotional responses in TB is multifaceted. TB is primarily a respiratory disease but the impact extends beyond the lungs and can affect various physiological systems, including the central nervous system (CNS). Serotonin is a neurotransmitter commonly associated with mood regulation. Research suggests that TB infection may alter serotonin levels in the CNS, potentially contributing to mood disturbances such as depression and anxiety commonly observed in TB patients. The immune response to TB infection, inflammatory cytokines, and metabolic changes associated with the disease can influence serotonin synthesis, reuptake, and receptor expression, affecting mood regulation. Dopamine is another neurotransmitter involved in mood regulation, reward, and

motivation. TB infection and associated inflammation may affect dopamine neurotransmission changes in mood and emotional responses. Dysregulation of dopamine signalling has been implicated in psychiatric symptoms such as anhedonia (loss of pleasure), which can occur in TB patients. TB infection and associated neuroinflammation can disrupt glutamate homeostasis cause excitotoxicity and neuronal damage. Dysregulation of glutamatergic signalling may contribute to mood disorders and cognitive impairment in TB patients. TB infection and neuroinflammation may alter GABAergic neurotransmission, disrupting the balance between excitation and inhibition in the brain. Dysregulation of GABAergic signalling has been implicated in anxiety and other mood disorders associated with TB. TB infection can dysregulate the HPA axis aberrant cortisol levels and stress responses, which may contribute to mood disturbances in TB patients.[19]

6. Interplay Between Psychological Factors and Gene Metabolism

Genetic predispositions to TB susceptibility and severity have been extensively investigated, the genetic basis of psychological factors in TB, such as anxiety, depression, and coping mechanisms, is less well understood. Though some preliminary studies suggest potential candidate genes that may be involved in the psychological response to TB.

6.1. SERT Gene (SLC6A4)

The serotonin transporter gene (SERT), encoded by the SLC6A4 gene, regulates the reuptake of serotonin a neurotransmitter implicated in mood regulation. Variants of the SERT gene have been associated with anxiety and depression in various populations. Research investigating the role of SERT gene polymorphisms in TB patient's psychological well-being and treatment outcomes could provide insights into the genetic basis of mood disorders in TB.

6.2. BDNF gene

Brain-derived neurotrophic factor (BDNF) is involved in neuronal survival, growth, and differentiation, and it plays a crucial role in mood regulation and stress response. Genetic variations in the BDNF gene have been linked to psychiatric disorders such as depression and anxiety. Investigating the association between BDNF gene polymorphisms and psychological distress in TB patients could shed light on the genetic mechanisms underlying mood disorders in TB.

6.3. Cytokine genes

Cytokines are signalling molecules involved in immune responses and inflammation. Dysregulation of cytokine levels has been implicated in the pathophysiology of both TB and mood disorders. According to certain research, short-term laboratory stress results in elevated concentrations of proinflammatory cytokines (IL-6, IL-1β, and TNF-α) in the bloodstream. It is interesting to note that stimulated responses were seen before circulating responses, suggesting that elevated circulating concentration may be a result of immune cells producing more cytokines in reaction to stress. Monocytes and macrophages are the main immune cells that produce these pro-inflammatory cytokines. Microbial products, such as LPS, attach to these cell's toll-like receptors (TLRs) during infection, encouraging the production of TNF-α and IL-1β, which in turn trigger the release of IL-6.[20]

6.4. HPA axis genes

Cortisol is released when IL-6 stimulates the hypothalamic-pituitary-adrenal (HPA) axis.[21] The hypothalamic-pituitary-adrenal (HPA) axis regulates the body's response to stress, and dysregulation of the HPA axis has been implicated in mood disorders such as depression and anxiety. Genes involved in the HPA axis, including corticotropin-releasing hormone (CRH), corticotropin-releasing hormone receptor 1 (CRHR1), and glucocorticoid receptor (NR3C1), may influence susceptibility to stress-related psychiatric symptoms in TB patients.

7. Epigenetic Mechanisms Mediating Psychological Factors in TB

Epigenetic modifications play a crucial role in mediating the relationship between psychological factors and gene expression in TB. DNA methylation is a common epigenetic modification that involves the addition of methyl groups to cytosine residues in DNA, typically occurring at CpG dinucleotides. Changes in DNA methylation can alter gene expression by modulating the accessibility of DNA to transcription factors and RNA polymerase modulate the expression of immune response genes, inflammation, and TB pathogenesis. Histone modifications including acetylation, methylation, phosphorylation and ubiquitination regulate chromatin structure and gene expression. Psychological factors can influence histone modification patterns in TB patients, impacting the accessibility of DNA and the recruitment of transcriptional machinery to specific gene loci. Changes in histone modifications can modulate the expression of genes involved in immune function, stress response and TB susceptibility. Psychological factors can influence the expression of ncRNAs in TB patients lead alterations in gene expression profiles and cellular pathways involved in immune response and TB pathogenesis. Dysregulation of ncRNAs can contribute to TB susceptibility disease progression, and treatment outcomes. Epigenetic modifications represent a mechanism

Table 1: Previous research findings showing comparatively higher rate of depression among TBpatients [10]

Country	Year	No. of samples	Tool used for depression assessment	Prevalence	Type of TB	Quality score of NOS	
Pakistan	2007-2008	65	HADS	36.9	MDR-TB	Low	Amir et. Al. [22]
India	2018	130	HAM-D	-	MDR-TB	High	Singh V et al. [23]
Ethiopia	2017	415	PHQ9	31.1	TB	High	Molla et al. [24]
Ethiopia	2017	403	PHQ9		TB	High	Dasa et al. [25]
Ethiopia	2015	657	PHQ9	54	TB	High	Ambaw et al. [26]
Ethiopia	2014	417	HADS	43.3	TB	High	Duko et al. [10]
Cameroon	2015	265	PHQ9	61.1	TB	High	Kahbila et al. [27]
Nigeria	2010	88	HDRS	45.5	TB	Low	Ige et al. [28]
Nigeria	2013-2015	371	PHQ9	30	TB/HIV	High	Larson et al. [29]
Nigeria	2008	65	PHQ9	30	TB	High	Baba et al. [30]
Brazil	2013	86	HADS	31.4	MDR-TB	Low	Dos et al. [31]
India	2012-2014	100	PHQ9	16	TB/HIV	Moderate	Mrinalini et al. [32]
India	2014-2015	100	HADS	55	MDR TB	Moderate	Chandra et al. [33]
India	2009-2011	200	HDRS	39.5	TB	Moderate	Arjun et al. [34]
India	2016	106	BDI-II	50	TB	Moderate	Dahiya et al. [35]
India	2015	100	BDII	35	TB	Low	Kumar et al. [36]
Turkey	2014-2015	208	HADS	60.5	TB	Moderate	Yilmaz et al. [37]
Pakistan	2013	213	HDRS	65.5	TB	High	Mahreen et al. [38]
Pakistan	2014	100	PHQ9	56	TB	Moderate	Amreen et al. [39]
Pakistan	2007	108	HADS	46.3	TB	Moderate	Hussain et al. [40]
Pakistan	2015	83	HDRS	49.4	TB	Low	Ahmed et al. [41]
Pakistan	2012-2013	289	HDRS	69.55	MDR-TB	High	Javaid et al. [42]
Pakistan	2009	60	BDII	80	TB	Low	Anwar et al. [43]
China	2014-2015	1252	PHQ9	16	TB	Moderate	Wang et al. [44]
India	2012	110	PHQ9	49	TB	Moderate	Basu et al. [45]
India	2017-2018	120	PHQ9	49	TB	Moderate	Ravi et al. [46]

through which psychological factors interact with genetic predispositions to influence TB susceptibility and disease outcomes. Stress, depression and other psychological factors can modulate epigenetic processes and change the gene expression profiles that may increase susceptibility to TB infection exacerbate disease progression or affect treatment response. Genetic variations may influence individual susceptibility to the effects of psychological factors on epigenetic regulation doing inter-individual variability in TB outcomes.

8. Gene-Environment Interactions

Genetic predispositions can interact with environmental factors to shape psychological responses to TB in numerous ways. Certain genetic factors may predispose individuals to heightened stress responses, anxiety, and depression when facing the challenges of TB, such as stigma, isolation, and treatment side effects. Genetic variations can affect immune responses to TB infection and the neuroinflammatory processes involved in the host's response to the disease. Dysregulated immune responses and neuroinflammation can contribute to mood disturbances, cognitive impairments, and other psychological symptoms in TB patients. Genetic factors influencing immune function and neuroinflammatory pathways may interact with environmental stressors to exacerbate psychological responses to TB. Neurotransmitter systems such as serotonin, dopamine, and gamma-aminobutyric acid (GABA) play critical roles in mood regulation and can be affected by both genetic and environmental factors. Interactions between genetic predispositions and environmental stressors may dysregulate neurotransmitter function, contributing to mood disorders and emotional disturbances in TB patients. Epigenetic modifications, which are influenced by both genetic and environmental factors, can modulate gene expression patterns underlying psychological responses to TB. Environmental stressors associated with TB such as social stigma, poverty, and treatment challenges, can induce epigenetic changes that affect neural circuitry, stress responses, and mood regulation. Genetic predispositions may interact with environmental factors to shape epigenetic profiles, influencing susceptibility to psychological distress and mental health outcomes in TB patients. Psychosocial factors such as social support, coping strategies, and resilience can moderate the impact of genetic predispositions on psychological responses to TB.

9. Conclusion

The relationship between psychological factors and gene metabolism in TB is intricate and multifaceted. Psychological factors like stress, anxiety, and depression can influence gene metabolism in TB patients through various mechanisms. These factors can alter gene expression patterns, epigenetic modifications, and immune responses, thereby impacting TB susceptibility, disease progression, and treatment outcomes. Psychological factors can modulate the expression of genes involved in immune function, inflammation, and stress response pathways. For instance, stress can activate signalling pathways regulating gene transcription changes in cytokine production, immune cell activation, and inflammation in TB patients. These modifications may influence immune cell function, host-pathogen interactions, and TB pathogenesis. Psychological factors can impact immune responses to TB infection, including innate and adaptive immunity. Stress-induced alterations in immune function may affect the host's ability to control TB infection increasing susceptibility to active disease or impairing treatment responses. Psychological stressors activate neuroendocrine pathways such as the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, influencing gene metabolism and immune function in TB patients.[47] Dysregulation of these pathways may contribute to immune suppression, inflammation, and disease progression. The relationship between psychological factors and gene metabolism in TB is bidirectional and complex. Psychological stressors influence gene expression, epigenetic regulation, immune responses, and neuroendocrine pathways, which in turn can impact TB susceptibility, disease severity, and treatment outcomes. Understanding this relationship is crucial for developing targeted interventions to address the mental health needs of TB patients and improve overall treatment outcomes. There is a pressing need for integrated approaches that consider both psychological and genetic factors in TB management. By addressing these factors together, clinicians and researchers can improve our understanding of TB pathogenesis, personalize treatment approaches, and enhance overall patient care and outcomes.

10. Abbreviations

NOS, Newcastle–Ottawa scale; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression Rating Scale; PHQ9, Patient Health Questionnaire-9; HDRS, Hamilton Depression Rating Scale; BDI-II, Beck's Depression Inventory-II, TB, Tuberculosis; MDR-TB, Multidrug resistant tuberculosis; HIV, Human acquired deficiency syndrome.

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12. Conflict of Interest

None.

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