VOLUME - 10, ISSUE - 08, AUGUST- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Psychiatry

A COMPARATIVE STUDY OF TNF-α AND IL-6 IN DEPRESSION PATIENTS WITH AND WITHOUT SUICIDAL BEHAVIOUR

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ABSTRACT

Introduction: Suicide is one of the leading causes of death around the world and tragically the 2nd leading cause of death in young population. Currently there are no clinically relevant predictors for suicide. Tumour Necrosis Factor α (TNF-α) is a cytokine produced in response to acute inflammation by macrophages, Interleukin 6 (IL-6) is another cytokine produced rapidly in response to infections and tissue injuries. Many studies have assessed the importance of other factors, but research lacks for inflammatory markers especially in real world designs. **Aims:** To compare TNF-α and IL-6 levels between depression patients with and without suicidal behaviour. **Methodology:** We compared 30 patients each of depression with and without suicidal behaviour cross sectionally, ICD10 was used for diagnosis. Hamilton Depression Rating Scale (HDRS-17), Suicide behaviour Questionnaire- Revised (SBQ-R), were applied for assessment of depression and suicidality. TNF- α and IL-6 was measured after blood sampling and proper storage protocol with autoanalyzer. **Results:** TNF- α levels were significantly higher in the depression with suicidal behaviour group (58.1 ± 57.5 pg/ml) and corelated positively HAM-D (r=0.43, p=0.001) and SBQ-R (r=0.63, p=0.001) scores with **Conclusion:** patients of depression with suicidal behaviour relates to the elevated TNF-α levels rather than depression alone. Using the findings of our study we hope that TNF-α will be able to serve as a potential biomarker for suicide. IL-6 findings were equivocal.

KEYWORDS :

INTRODUCTION:

Depression is one of the leading psychiatric disorders in the world and causes a huge impact on daily functioning along with adding to the global burden. Lifetime prevalence of major depression in the India is 21% of women and 11%–13% of men.[1] Suicide is one of the leading cause of death around the world and tragically the 2nd leading cause of death in young population.[2] Faster recognition of suicidal behavior is key for the prevention and optimal treatment of suicide. Currently there are no clinically relevant predictors of response for depression patients to one antidepressant compared to others despite of contrary claims and recent pharmacological advancements due to which clinicians have to wait for clinical response.[3-4]

Tumour Necrosis Factor α (TNF-α) is a cytokine produced in response to acute inflammation by macrophages or monocytes which is responsible for a varied range of signalling events within cells and can lead to apoptosis in various tissues. The protein is also important for protecting against infection and cancers.[5] Interleukin 6 (IL-6) is another cytokine produced rapidly in response to infections and tissue injuries which helps in body defense through the stimulation of acute phase responses, haematopoiesis, and immune reactions. Initially separate functions of IL-6 were observed, and nomenclature was based on their biological activity. The expression of IL-6 is controlled genetically, and dysregulated rise of IL-6 creates a pathological effect on chronic inflammation.[6]

Numerous studies have supported the hypothesis that assessment of inflammatory marker profile of suicidal patients may be vital for improved prediction of suicidal behaviors and identification of novel therapeutic strategies to prevent and treat suicidality.[7]

As per newer evidence, inflammatory markers may indicate abnormalities in the kynurenine pathway, leading to an increased production of quinolinic acid, which agonizes N-methyl-D-aspartate (NMDA) receptors causing neurotoxic effects which can potentially contribute to the onset and pathogenesis of affective disorders and suicidality. [8-10]

Many studies have assessed the importance of race, body mass index (BMI), gender and depression as factors influencing serum TNF α and IL-6 levels in psychiatric populations, although these factors weren't studied, and findings replicated in real world designs. In the present study, we explore a clinical inflammatory marker TNF - α and IL-6 in depressive patients following suicidal behaviour with the goal of obtaining a significant correlation between TNF - α and IL-6 and suicidality.

METHODOLOGY:

This was a cross sectional hospital-based study to compare the TNF-α and IL-6 levels among depression patients with and without suicidal behaviour conducted in MGM Medical College Indore after approval from institutional scientific and ethics committee. The case group included depression patients exhibiting suicidal behaviour like suicidal ideation or suicidal attempt. The control group had depression patients without any suicidal behaviour or history of suicidal attempt. Patients who met the diagnosis of severe depression according to diagnostic criteria for research of International Classification of Diseases -10th edition (ICD-10 DCR) and were drug naïve or drug free for at least 3 months and aged between 18-60 years were included in the study. Patients having any other major physical, endocrinology or psychiatric co morbidities, current scheduled use of, use of anti-psychotics, anti-depressants, pregnancy were excluded. Patients on interferon—based immunotherapy, medical, inflammatory and neurological comorbidities were also excluded due to their modifying effects on TNF -α and IL-6 levels. Subjects were taken from MGM Medical College after fulfilling the inclusion criteria. After complete description of the study to the subjects, written informed consent was obtained from all participants. A detailed physical examination was done to rule out major medical or neurological illness. After that clinical assessment of patient group was done using HDRS, SBQ-R scales. Blood samples of all groups were drawn after explaining the procedure and were collected in a clot activator tube. Serum was processed from the sample via centrifuge machine and the serum was analysed for TNF-α and IL-6 with Automated analyser using

enzyme linked immune sorbent assay (ELISA) and later results were analysed.

RESULTS-

Table 1: Sociodemographic Variables Of The Patients

	Depression with suicidal behaviour (N=60)	Depression without suicidal behaviour (N=60)
Age(mean) in years	28.0 years	32.6 years
Males Females	28 (46.6%) 32 (53.3%)	27 (45%) 33 (55%)
Marital status in %:		
Married	50%	56.6%
Unmarried	45%	41.6%
Divorced	1.7%	1.7%
Widowed	1.7%	0%
Remarried	1.7%	0%
Religion in %:		
Hindu	73.3%	66.7%
Muslim	26.7%	33.3%
Education in %:		
Illiterate	11.7%	23.3%
Primary (5^{th})	20%	15%
Middle(8^{th})	21.7%	10%
High School	15%	20%
Inter	10%	8.3%
Diploma/Graduate/Post graduate Professional	21.7%	23.3%
Socioeconomic		
Low	63.3%	58.4%
Middle	33.3%	36.6%
High	3.4%	5%
Occupation		
Employed	32%	40%
Unemployed	68%	60%
Family type		
Nuclear	78.3%	71.7%
Extended/ Joint.	21.7%	28.3%
Locality		
Urban	76.7%	73.3%
Rural	23.3%	26.7%

In comparison to the depression without suicidal behaviour the depression with suicidal behaviour had younger age of onset (28 years), more male (52%), married (62%), Hindu faith (73.3%), unemployed (68%), urban (76%) locality-based subjects. However, there were fewer illiterate (11.7%) and low socioeconomic subjects (74%) in the suicidal group than the non-suicidal group.

Table 2: Description Of Duration Of Illness (months) In Study Participants In Case And Control Groups.

	N	Minimum	Maximum	Mean	Std. Deviation
Suicidal depression patients	60	1	18	6.2	3.3
Non-Suicidal depression patients	60	2	24	7.8	4.2

The case group had a mean of duration of illness of depression as 6.2 ± 3.3 month while the control group had a mean of 7.8 ± 4.2 months as mean.

The maximum duration in case group and control group were 18 and 24 months respectively while minimum duration was 1 months in depression with suicidal behaviour and two months in depression without suicidal behaviour.

Table 3: Description Of Age Of Onset Of Depression (years) In Study Participants In Case And Control Groups

	N	Minimum	Maximum	Mean	Std. Deviation
Suicidal depression patients	60	18	56	27.6	10.1
Non-Suicidal depression patients	60	20	59	31.8	8.5

The mean age of onset for case group was 27.6 ± 10.1 years while that for control group was 31.8 ± 8.5 years.

Table 4: Clinical Characteristics Of The Depression Patients (Continuous Variables)

Variables	Suicidal depression patients Mean± SD N=60	Non-Suicidal depression Patients Mean± SD N=60	t value	p value
Age of onset of illness (in years)	27.6 ± 10.1	31.8 ± 8.5	2.50	.01
Duration of illness (in months)	6.2 ± 3.3	7.8 ± 4.2	2.3	.02
HAM-D SCORES	24.6 ± 4.2	23.9± 3.3	1.0	.30
SBQ-R SCORES	12.4± 2.3	-	-	-

The mean age of onset of illness of depression with suicidal behaviour patients was 27.6± 10.1 years. The mean age of onset of illness of depression without suicidal behaviour patients was 31.8± 8.5 years. The mean duration of illness of depression with suicidal behaviour patients was 6.2± 3.3months. The mean duration of illness of depression without suicidal behaviour patients was 7.8± 4.2months.

On comparison of HDRS score the depression with suicidal behaviour group had a mean HDRS score of 24.6 ± 4.2 while depression without suicidal behaviour group had a mean of 23.9 ± 3.3. Both mean scores are representative of severe depression as per Hamilton rating scale and our inclusion criteria, however both means did not differ statistically. SBQ-R scores for the suicidal behaviour group was 12.4± 2.3.

Table 5: Comparison Of IL-6 Between Depression Patients With Suicidal Behaviour And Non-suicidal Behaviour

IL-6 (pg/ml)	Depressionwith suicidal behaviour (N= 60)	Depressionwithout suicidal behaviour (N= 60)
Mean	15.1	14.4
N	60	60
Std. Deviation	2.2	2.6
t value	1.4	
p value	0.15	

The mean IL-6 for depression with suicidal behaviour was 15.1 ± 2.2pg/ml which is considered as high value as per our criteria for cut off (2 pg/ml). IL-6 values for depression without suicidal behaviour was 14.4 ± 2.6pg/ml which is also higher than cut-off, and the means did not differ significantly. Depression with suicidal behaviour patient group has shown slightly higher IL-6 mean scores than non-suicidal group of depression however it was not statistically significant.

Table 6: Comparison Of TNF -α Between Depression Patients With Suicidal Behaviour And Depression Patients Without Suicidal Behaviour.

TNF -α(pg/ml)	Depression with suicidal behaviour (N= 60)	Depression without suicidal behaviour (N= 60)
Mean	58.1	40.2

Std. Deviation	57.5	40.1
t value	1.99	
p value	0.04	

*Statistically significant

The case group had a mean TNF -α value of 58.1 ± 57.5 pg/ml while control group had a mean of 40.2 ± 40.1pg/ml. Suicidal attempt patient group has shown higher TNF -α levels than depression patient without suicidal behaviour which was statistically significant. Both groups have high value of TNF as per our criteria for cut off (≥8 pg/ml).

Table 7: Chi Square Test For TNF –α (low & high) Between Depression With Suicidal Behaviour And Depression Without Suicidal Behaviour

		TNF -α result		Total
		TNF -α low (value <8 pg/ml)	TNF -α high (value ≥ 8pg/ml)	
Suicidal depression	Count	16	44	60
	Expected count	21.5	38.5	60.0
Non-suicidal depression	Count	27	33	60
	Expected count	21.5	38.5	60.0
Total	Count	43	77	120
	Expected count	43.0	77.0	120.0
Pearson chi-square	4.38			
p value	0.03			
Cramer's V	0.4			

The TNF -α values above and below normal range which is 8 pg/ml as per existing literature and methodology, the chi square test was statistically significant implying that depression patients with suicidal behaviour have more TNF–α above cut off range than depression without suicidal behaviour.

In context of IL-6 since all samples in both groups had values> 2 pg/ml which is set as cut off for normalcy, test of significance did not provide any useful result.

Table 8: Correlation Of TNF-α With HAM-D Scores In Patients Of Depression With Suicidal Behaviour And Depression Without Suicidal Behaviour

	HAM-D suicidal depression		HAM-D non-suicidal depression		SBQ-R suicidal behaviour	
TNF-α	r	p	r	p	r	p
	.43	.001*	.48	.001*	.63*	.001
IL-6	.30	.21	.23	.31	.06	0.22

There is a statistically significant strong positive correlation between HAM-D scores and TNF-α levels in depression with suicidal behaviour group, while the depression without suicidal behaviour group also had a positive correlation between TNF and HAM-D which was statistically significant. There is a statistically significant moderate positive correlation between SBQ-R scores and TNF-α levels in depression patients with suicidal behaviour.

There is a weak positive correlation between HAM-D scores and IL-6 levels in both case and control groups however the correlation is not statistically significant. There is a weak correlation between SBQ-R scores and IL-6 levels in depression with suicidal behaviour group which was not statistically significant.

DISCUSSION:

The present study was conducted with the aim of assessment of IL-6 and TNF-α levels in Depression Patients with Suicidal behaviour and without suicidal behaviour. Depression races ahead of other disorders in terms of disability created and morbid condition generated other than indirect loss to socio-economic conditions this adding to global burden of disease. A psychiatric illness, especially major depressive disorder (MDD) or bipolar affective disorder is a major risk factor of suicide as 90% of suicide completers suffer from some form of psychiatric illness.[11] Inflammatory markers can be linked to suicidality, among which IL-6 & TNF – α is thought to play an important role. Earlier studies have shown a relation between suicidal behaviour and inflammatory markers. (Courtet, et al 2015 [12]; Gibbs, et al 2016 [13]; Mudgal [14], Gambi et al,2005[15], Park et al,2017[16]).

The sociodemographic interpretation of the sample displayed the mean age of case group was 28.0 ± 10.4 years while that of control group was 32.6 ± 8.7 years. The number of female patients were higher in both, the case group (53.3%) and the control group (55%). Most participants in both the case (50%) and control (56.6%) groups were married and Hindu in both case (73.3%) and control (66.7%) groups. It was observed that patients in the less educated group were more likely to exhibit suicidal behaviour. Low socio-economic income groups were found to be the majority in both case (63.3%) and control groups (58.4%). The distribution of case (76.7%) and control (73.3%) sample were urban in majority and had a predominance of nuclear family distribution in case (78.3%) and control group (71.7%). (Table 1)

The mean duration of illness (Table 2) of depression with suicidal behaviour patients was 6.2 ± 3.3 months. The mean duration of illness in depression without suicidal behaviour patients was 7.8 ± 4.2 months. This is keeping with the mean duration of depression in most literature [17]. So that, we suggest the depression with suicidal behaviour patients reported to the health-care settings early as compared to depression without suicidal behaviour patients.

All the samples of our study were diagnosed with major depression had a mean age of onset of 29.7 years (Table 3). The case subjects had a mean age of onset of 27.6 ± 10.1 years. while the control group had a mean age of 31.8 ± 8.5 years, it implies that patients of depression exhibiting suicidal behaviour had earlier onset of illness, similar results were obtained by Pal et al.[18], Dunjic-Kostic et al.[19], Islam et al.[20] Dar et al.[21] The younger age of onset for suicidal depression is in concordance with Kessler et al [22] who reported that age <25 years is a risk factor for suicide, while Yang et al.[23] also reported earlier age of onset in depression patients with suicidal behaviour.

We found no statistically significant difference between HAM-D scores of both groups. The SBQ-R mean scores of 12.4 ± 2.3, scores more than 8 denotes a high suicidal risk and the same is validated in our study. (Table 4)

On comparison of IL-6 levels between depression patient with suicidal behaviour and depression without suicidal behaviour patients (Table 5) it was revealed that the mean IL-6 for depression with suicidal behaviour was 15.1 ± 2.2 pg/ml which is considered as high value as per our criteria for cut off (2 pg/ml). IL-6 values for depression without suicidal behaviour was 14.4 ± 2.6pg/ml which is also higher than cut-off, thus did not differ significantly. Depression with suicidal behaviour patient group has shown slightly higher IL-6 mean scores than non-suicidal group of depression however it was not statistically significant. This finding is in agreement with Vargas et al. [24] and Gabbay et al. [25] who reported no significant change in IL-6 levels in suicidal patients. In context of IL-6 since all samples in both groups had values> 2 pg/ml which is set as cut off for normalcy, test of significance did not provide any useful result hence IL-6 results were equivocal.

TNF -α levels between depression patient with suicidal

behaviour and depression patient without suicidal behaviour were compared (Table 6) and it was noted that the depression with suicidal behaviour group had a mean TNF -α value of 58.1 ± 57.5 pg/ml while depression without suicidal behaviour group had a mean of 40.2± 40.1pg/ml. Suicidal behaviour group has shown higher TNF-α levels than depression patient without suicidal behaviour which was statistically significant. Both groups have high value of TNF as per our criteria for cut off (≥8 pg/ml). In concordance with our study Kim et al [26], Mendlovic et al [27], Janelidze et al. [28], Pandey et al. [29] and O'Donovan et al. [30] also found higher levels of TNF-α in suicidal behaviour. Gabbay et al.[25] however found contrasting results where TNF- α levels were found to be lower in the suicidal depression group than healthy controls and non-suicidal group.

The TNF -α values above and below cut off range which is set as 8 pg/ml as per existing literature and methodology in depression patients with and without suicidal behaviour for the current study. We found that the chi square test was statistically significant (Table 7) implying that depression patients with suicidal behaviour have more TNF–α samples above cut off range than depression without suicidal behaviour and the difference was statistically significant. Hence TNF- α can be considered a novel biomarker which is indicative of suicide in context of depression. Most of the previous studies [26, 28-31] have evaluated TNF- α in context of suicide, our study is unique in design for evaluating TNF- α levels in patients of depression with suicidal behaviour with those of depression without suicidal behaviour hence removing the confounding effect of depression over TNF- α.

Summating the results, we can conclude that in patients of depression with suicidal behaviour TNF- α can serve as a biomarker while results for IL-6 were equivocal. The study results build up on the notion that suicidal behavior in presence of MDD encompasses immune system dysregulation. Particularly, the role of increased TNF-α is suggested. These findings require replication in a larger sample of medication-free adults.

There is a statistically significant strong positive correlation between HAM-D scores and TNF-α levels in depression with suicidal behaviour group, while the depression without suicidal behaviour group also had a positive correlation between TNF-α and HAM-D which was statistically significant (Table 8). As the severity of depression rises TNF- α levels also increase, our results are backed up by Dowlati et al. [31].

There is a statistically significant moderate positive correlation between SBQ-R scores and TNF-α levels in depression patients with suicidal behaviour (Table 20). This finding predicates the notion that as suicidality increases there is a rise in TNF- α levels. We quantified suicidal behaviour using SBQ-R scale which has a linear scoring and a cut off score of ≥ 8 indicative of high suicidal risk. We found that patients who scored high on the SBQ-R had significantly higher TNF- α levels as well. The kyneurine pathway describes the presence of inflammation as a risk factor for suicidality and the same finding is presented by our study. This finding is novel in its origin as the patients of suicide with depression having elevated TNF- α has not been replicated with our study design and population group. The IL-6 levels had a weakly positive correlation with HAM-D and SBQ-R which was not statistically significant (Table 8).

CONCLUSION:

The IL-6 levels were elevated above cut off levels in both suicidal and non-suicidal depression group and the test of significance was unfruitful which implies that IL-6 is not a very specific marker for suicide rather is found to be elevated even in context of depression. TNF-α levels were significantly higher in the depression with suicidal behaviour group than the non-suicidal depression group and the test of significance substantiates this finding. TNF-α levels also correlate positively with SBQ-R scores which is a quantitative indicator of suicidal behaviour, which has a huge impact on prediction of suicide and its prediction in future. IL-6 on the contrary did not correlate at any significant level with suicidal behaviour secondary to which we can construe as per our findings that IL-6 has a very erratic connection with suicide and might not be used as a specific marker for prediction or assessment of suicidal behaviour in context of depression. Keeping in view of all the above findings we can conclude that patients of depression with suicidal behaviour relates to the elevated TNF-α levels rather than depression alone. Using the findings of our study we hope that TNF-α will be able to serve as a potential biomarker for suicide.

Limitations:

There is an absence of prospective follow-up which can assess correlation of depression & suicide scores with later TNF-α and IL-6 levels. Inflammatory marker TNF-α and IL-6 levels could be altered by other inflammatory conditions and increasing age. Despite a large sample inclusion for a study of such design the sample size could still be increased with a longer study duration. We relied on self-reported history of suicidal ideation as source of information future studies could include other methods.

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