REVIEW ARTICLE

Is depression a somatic disease or a psychiatric disorder?

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Abstract

Depression has long been a major target of psychiatry. The number of patients with depression is increasing year by year, especially in developed countries, and it continues to be one of the most urgent matters for mental health professionals. Efficient treatment measures and useful means of prevention of depression are highly anticipated from the field of psychiatry, but difficult problems in diagnosing and defining depression remain. Since the introduction of the operational diagnostic criteria of *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5) in 2013, the diagnostic window for depression has been significantly expanded. Depression from physical cause and depression due to psychosocial cause are no longer distinguished, a situation which may actually hinder the understanding of the pathogenesis of depression. In this review article, inflammation and insulin resistance are used as examples of the physical causes of depression, demonstrating that some depression can be understood as a physical disease. Vascular depression is a physically induced form of depression seen in elderly people, but diagnosis is complicated by depression also being caused by psychosocial factors resulting from various loss experiences associated with old age. Finally, to demonstrate the heterogeneity of depression, we propose a model in which depression develops due to an increase in the amplitude of mood swings, a decrease in the baseline level of mood swings, and a narrower allowable range of mood swings, which can be explained by physical, psychological and social factors, respectively.

"Depression is the most unpleasant thing I have ever experienced.... It is the inability to imagine being well again. It is a lack of hope. The emotional depression of major depression is very different from feeling sad. Sadness is a healthy feeling, a need to feel, but depression is quite different" (Rowling JK, 2000).

Key words: *major depressive disorder, somatic disease, psychiatric disorder, inflammation, insulin resistance*

Introduction

In traditional German psychiatry, the three major psychiatric disorders were considered to be depression, schizophrenia, and epilepsy. Depression was the main target of psychiatry, and with consideration of its pathology, severity, causative factors and possible interventions, it was classified as either endogenous, neurotic, or reactive depression.

Pharmacotherapy for depression became available in the 1950s, with the introduction of tricyclic and tetracyclic antidepressants. Subsequently, monoamine oxidase inhibitors (MAOIs), serotonin selective reuptake inhibitors (SSRIs), and serotonin-noradrenaline reuptake inhibitors (SNRIs), and other drugs with various pharmacological actions have been introduced as pharmacotherapy for depression. More recently, bupropion, esketamine and psilocybin have come under consideration for clinical use. However, approximately one third of patients still have a poor response to pharmacotherapy with antidepressants, and the augmentation therapy in combination with lithium, thyroid hormone, or atypical antipsychotics has been used to treat patients with depression who have been resistant to treatment.

In addition to pharmacotherapy, biological therapies such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) have been used, and these brain stimulation methods have evolved along with functional brain imaging techniques. These include vagal nerve stimulation (VNS), deep brain stimulation (DBS), transcranial direct current stimulation (tDCS), and focused ultrasound (FUS). Psychotherapy, which includes cognitive therapy and interpersonal psychotherapy, has also been shown

to be an effective treatment for depression. Psychotherapy combined with hallucinogenic drugs such as lysergic acid diethylamide (LSD) and psilocybin has also recently been introduced.

The concept of depression in Japanese psychiatry has changed significantly over time, especially since the introduction of the American Psychiatric Association operational diagnostic system. The distinction between endogenous, neurotic, and reactive depression, which were emphasized in psychopathology in German psychiatry, has become less important. Depressive disorders according to *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5) were broadly classified into either major depression or chronic persistent depressive disorder. In addition to the increase in the number of patients with depression, there has been the widespread introduction of SSRIs and SNRIs. The side effects associated with the use of antidepressants has become less severe than in the past, meaning general physicians are now often responsible for treating mild cases of depression. In some cases, general physicians can participate in the treatment of the patients with depression with little psychiatric understanding of depression itself, and this may have undesirable results. The question of whether depression should be regarded as a physical or mental illness thus requires careful consideration.

There are currently growing suggestions about the involvement of chronic inflammation or insulin resistance (leading to diabetes mellitus) to pathogenesis of depression, which supports the notion of physical aspect of depression. There is also a movement to re-evaluate the old classification of depression (reactive, neurotic, endogenous). Depression is a general term used to describe depressed mood, whether pathological or not. In psychiatry, conditions that present with extreme depression have long been referred to by various names, including depression, melancholia, mood disorders, and major depressive disorder, but this article will discuss major depressive disorder (MDD) in reference to DSM-5.

1. Depression in traditional German psychiatry

Japanese psychiatry was developed under the influence of German psychiatry prior to the introduction of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) developed by American Psychiatric Association. In Japanese psychiatry, as in German psychiatry, depression was subdivided into three subtypes: reactive, neurotic, and endogenous depression (Table 1).

Reactive depression is defined as a depressive reaction that occurs after person is exposed to a strong psychogenic or stressful event. It can occur in any person who is exposed to sufficiently intense stress, and develops without any particular predisposition or personality problem in that person. Reactive depression occurs in response to stress, so recovery would come as a result of eliminating stress or psychogenic factors, and theoretically an effective treatment would be to eliminate these causative factors by adjusting the subject's situation and their environment. Considering the nature of self-recovery of reactive depression, the psychopathological level is considered to be the mildest of the three subtypes.

Neurotic depression is a condition in which depressive symptoms appear when a person with a neurotic personality (predisposition) is exposed to stress (fruition factor), even if the stress is comparatively trivial in general terms. Innate neurotic personality is regarded as the main causative factor. Stress itself may therefore play a role in triggering the onset of depression. Considering the major role of personality in neurotic depression, the focal treatment modality was mainly psychotherapy. Psychotherapy is the first-line

Table 1. Subtypes of depression in traditional German Psychiatry

Subtype	Psychopathological level	External factor	Internal factor	Recommended intervention
Reactive	mild	++	−	Environmental adjustment
Neurotic	moderate	+	+	psychotherapy
Endogenous	severe	−	++	pharmacotherapy

Schizophrenia, depression, and epilepsy were regarded as the three main targets in German psychiatry. Depression (*Manische Depressives Irresein*) was sub-typed into endogenous, neurotic, and reactive depression according to psychopathology, severity, and causative factors. Subtyping of depression is utilized in clinical settings because each subtype implies effective intervention, environmental adjustment, psychotherapy, and pharmacotherapy, respectively.

treatment in an attempt to modify the behavioral stereotype of patients with neurotic depression.

Endogenous depression, meanwhile, is caused by unknown patient factors, and it may occur spontaneously in people without any psychogenic or neurotic predisposition. The level of psychopathology is profound, with intractable and recurrent nature. Pharmacotherapy with antidepressants is the first choice of treatment for endogenous depression.

2. Depression in *DSM*

In contrast to the German psychiatric concepts of depression, the DSM adopted an operative diagnostic criterion of depression. The operative procedures underlying DSM aim to eliminate speculation on the patient's psychopathological processes, so only objectively confirmable parameters such as epidemiological findings, symptom combinations, symptom course, risk factors, prognosis, and others are considered in diagnostic criteria. Reactive, neurotic, and endogenous depression are no longer distinguished.

Bereavement of a loved one induces a strong sense of grief and depression in many people. There has been much debate over whether bereavement reactions should be treated as a subtype of depression, but DSM-IV, published in 1994, treated bereavement reactions as a separate entity.

3. Depressive disorders according to DSM-5

The description of depressive disorders in DSM-5, published in 2013, changed significantly from those in DSM-IV, which was published in 1994 and updated in 2000. 'Depressive disorders' in DSM-IV was an umbrella term used to describe mood disorders which included both depression (corresponding to unipolar mood disorder) and bipolar mood disorder. Unipolar mania with elevated mood, unipolar depression with depressed mood, and mania/depression with alternating elevated and depressed mood were understood as change of mood, so these disorders are classified into the single category of 'mood disorders' in DSM-IV. Recent findings in psychiatry, particularly from the results of biological research of the pathogenesis of mood disorders, have led to mood disorders and bipolar disorders being differently categorized. For example, analysis of molecular genetics of risk genes of mood disorders has clearly demonstrated that the genetic risk of bipolar disorders is different from that of depressive disorders, suggesting different calibration of genes associated with the risk of their development. Bipolar disorder and related disorders were removed from the framework of mood disorders and became independent items in DSM-5.

The depressive disorders group in the DSM-5 comprises severe mood dysregulation, major depression, persistent depressive disorder, premenstrual dysphoric mood disorder, substance- or drug-induced depressive disorder, depressive disorder due to other medical factors, other identified depressive disorders, and other unspecified depressive disorders. Common features of this group in the DSM-5 are the presence of a sad, empty, or easily offended mood, accompanied by physical and cognitive changes that significantly affect an individual's ability to function. Severe mood regulation disorder is a disorder that affects children, premenstrual dysphoric mood disorder is specific to women, and substance and drug-induced depressive disorder is for known causes. The actual broad areas of focus are therefore major depressive disorder and persistent depressive disorder.

3-1. Major depressive disorder

Depression is a condition in which depressive symptoms are severe, accompanied by significant distress due to the symptoms, last longer than two weeks, and cause impairment of daily functioning. Symptoms of depression can be roughly classified into abnormal emotional functioning, abnormal psychomotor functioning, and abnormal physical functioning. Abnormalities in psychomotor function include anxiety and agitation, decreased level of interest and concern, decreased energy, thoughtlessness, impaired decision-making and judgment, and fatigue/easiness.

Many patients with major depressive disorder have recurrent depressive episodes. These consist of a prodromal phase, a polar phase, and a remission phase. During the prodromal phase, the patient loses interest in things, becomes distracted, and lacks perseverance, and typically has psychosomatic complaints such as a feeling of tiredness, disturbed sleep, and loss of appetite. As depression becomes more severe, the patient may develop difficulty in thinking clearly, lose self-confidence, become agitated, and have severe fatigue, insomnia, weight loss, and loss of libido. In the extreme phase of depressive episodes, the patient becomes severely depressed, unable to seek help from others, and has significant emotional distress in place of agitation, resulting in self-doubt and potentially suicidal ideation. The mood remains depressed almost all day and spontaneity is lost. In remission, with signs of improvement, the range of mood swings increases, and the patient becomes agitated, nervous, and more active, but the

mood remains depressed. The patient then begins to feel better for longer periods of time, becomes more interested in things again, gains confidence, has hope for a cure, and is able to work.

3-2. Persistent depressive disorder

Persistent depressive disorder is the successor to the DSM-IV concept of mood dysphoria, in which there is chronic persistence of mild depressive symptoms that do not meet the criteria for a depressive episode. Originally, the term 'mood dysphoria' was used in traditional German psychiatry to describe neurotic depression, and the basic presentation of persistent depressive disorder, which inherited the mood dysphoria concept, is the same as that of mood dysphoria. Persistent depressive disorder differs from mood modulation disorder in that it includes a chronic course of depression superimposed in part. Persistent depressive disorder, by definition, includes depressive episodes superimposed on the illness of mood dysphoria for a period of two years or longer. It is therefore a broad concept that includes chronic depression in terms of persistence, compared with the mood disorder, which excluded chronic depression.

4. Inflammation and depression

The cytokine theory of depression was proposed in the 1990s as the 'macrophage theory of depression' (Smith, 1991). It was studied intensively by many researchers including by M. Maes, who reported that biomarkers reflecting inflammation, such as cytokine (IL-6, TNFα) and C-reactive protein (CRP) levels, are elevated in the peripheral blood of depressed patients (Maes, 2007, 2011). Although evidence from many experimental and observational studies has suggested an association between inflammation and depression, the findings have not been organized into a common set of findings for all patients with major depression. We also reported elevated levels of soluble IL-6 receptors in the peripheral blood of patients with refractory major depression who do not respond to usual antidepressant treatment (Yamasaki, 2020), but there is no consensus understanding of which mechanisms of inflammation may induce major depression.

To understand this discrepancy, a meta-analysis (Frank, 2021) pooled data from 15 cohort studies, classified symptoms of depression into four domains (affective, cognitive, physical, and cognitive), and examined the correlation between inflammatory markers (CRP and IL6 levels) and symptoms in each domain. CRP/IL6 measurements and 24 symptoms were described. The overall CRP level of 56,351 subjects (mean age 57.8 years [*SD*=12.0], female ratio = 51.5%) was 0.89 mg/L (95% CI=0.85,0.94) and IL-6 level was 0.74 pg/mL (95% CI=0.70,0.78). The incidence of each symptom was distributed from suicidal ideation (1.1%) to sleep disturbances (21.5%), with a mean incidence of symptoms of 14.0%. A 1 SD increase in CRP levels was associated with an odds ratio of 1.18 for depression adjusted for age and gender (Model 1), indicating a correlation between inflammation and symptoms of major depression. However, the odds ratio decreased to 1.05 when adjusted for age, gender, education, comorbidities, and lifestyle (Model 5) (Table 1). By symptom, high CRP correlated with 6/7 items of physical symptoms, 2/3 items of cognitive function symptoms, 5/9 items of emotional symptoms, 2/4 items of self-emotional symptoms, and 1/1 item of self-harm symptoms. In Model 5, high CRP levels increased the odds ratios for four physical symptoms (appetite, helplessness, lethargy and sleep disturbances), two cognitive symptoms (attention difficulties and loss of interest), and one emotional symptom (depressed mood). By domain, high CRP levels showed a strong correlation with physical and cognitive symptoms, and a minimal relationship with emotional symptoms (Table 2).

This meta-analysis showed that systemic inflammation (high CRP) was clearly associated with a series of physical symptoms (appetite, fatigue, impotence, insomnia) and cognitive symptoms (apathy), but high CRP levels were not associated with emotional symptoms (annoyance, pessimism, fear, giving up on life). In patients with major depression, high levels of inflammatory markers correlate better with physical symptoms than emotional symptoms (Frank, 2021).

The results of this study suggest that, among the symptoms that support a diagnosis of major depression by DSM-5, somatic and cognitive symptoms correlate with inflammation. However, it is important to remember that the DSM-5 also requires the presence of either depressed mood or loss of interest and concern as a required emotional/psychiatric symptom. Although inflammation correlated with many of the physical symptoms in the DSM-5 diagnostic criteria items, it did not correlate with the underlying emotional and psychiatric symptoms.

The DSM-5 diagnostic criteria for major depression may be gradually beginning to diverge from the previous psychopathological understanding of depression. Inflammation is a reflection of physical illness and may be less likely to correlate with psychiatric symp-

Table 2. Unadjusted and serially adjusted cross-sectional association between C-reactive protein and 24 symptoms of depression (random-effects meta-analysis)

Outcome	N (participants)/ N (studies)	Crude Odds Ratio and 95% CI	Odds Ratio (95% CI) per 1 SD Higher CRP[a]				
			Model 1	Model 2	Model 3	Model 4	Model 5
Depression	56,220 / 15		1.18 (1.14–1.22)	1.15 (1.11–1.18)	1.16 (1.12–1.20)	1.06 (1.03–1.10)	1.05 (1.02–1.09)
Depressive symptoms							
Had crying spells	9,786 / 3		1.24 (1.00–1.53)	1.22 (0.98–1.51)	1.22 (0.99–1.51)	1.12 (0.92–1.36)	1.10 (0.94–1.30)
Changes in appetite[b]	34,615 / 10		1.23 (1.18–1.27)	1.20 (1.16–1.24)	1.21 (1.17–1.26)	1.12 (1.07–1.18)	1.14 (1.09–1.19)
Felt everything was an effort[b]	27,130 / 8		1.23 (1.12–1.36)	1.21 (1.11–1.32)	1.21 (1.10–1.34)	1.11 (1.04–1.19)	1.12 (1.04–1.21)
Thought you would be better off dead	22,420 / 5		1.22 (1.06–1.39)	1.18 (1.03–1.36)	1.18 (1.03–1.34)	1.10 (0.95–1.27)	1.07 (0.93–1.24)
Little interest in doing things[b]	31,000 / 6		1.21 (1.16–1.26)	1.18 (1.13–1.23)	1.19 (1.14–1.24)	1.10 (1.05–1.15)	1.09 (1.04–1.14)
Could not get going/loss of energy[b]	50,736 / 14		1.20 (1.16–1.24)	1.18 (1.14–1.23)	1.19 (1.14–1.23)	1.09 (1.06–1.13)	1.08 (1.05–1.12)
Feeling bad about yourself	22,420 / 5		1.18 (1.12–1.24)	1.15 (1.09–1.21)	1.15 (1.09–1.20)	1.05 (0.99–1.11)	1.03 (0.97–1.09)
Could not shake off the blues	9,786 / 3		1.16 (1.04–1.29)	1.14 (1.04–1.26)	1.16 (1.04–1.29)	1.03 (0.91–1.16)	1.03 (0.91–1.15)
People were unfriendly	12,195 / 5		1.15 (0.97–1.36)	1.11 (0.95–1.31)	1.14 (0.96–1.35)	1.07 (0.90–1.27)	1.03 (0.85–1.24)
Life had been a failure	9,786 / 3		1.15 (0.95–1.38)	1.14 (0.95–1.35)	1.15 (0.96–1.39)	1.06 (0.91–1.25)	1.07 (0.92–1.23)
Moving or speaking slowly or too fast	22,420 / 5		1.14 (1.07–1.22)	1.11 (1.04–1.19)	1.11 (1.04–1.20)	1.06 (0.98–1.13)	1.04 (0.97–1.11)
Felt lonely	27,130 / 8		1.13 (1.09–1.17)	1.10 (1.06–1.14)	1.12 (1.08–1.16)	1.05 (0.99–1.11)	1.04 (0.99–1.09)
Sleep problems[b]	55,165 / 14		1.13 (1.09–1.17)	1.11 (1.07–1.15)	1.11 (1.08–1.15)	1.06 (1.02–1.10)	1.05 (1.01–1.09)
Felt depressed	54,563 / 13		1.13 (1.09–1.18)	1.10 (1.06–1.14)	1.11 (1.06–1.16)	1.03 (1.00–1.07)	1.02 (0.98–1.06)
Trouble concentrating[b]	37,821 / 9		1.12 (1.07–1.18)	1.11 (1.05–1.16)	1.11 (1.06–1.16)	1.07 (1.02–1.11)	1.07 (1.01–1.13)
People dislike me	11,593 / 4		1.12 (0.90–1.39)	1.09 (0.88–1.35)	1.11 (0.90–1.35)	0.99 (0.78–1.25)	0.98 (0.78–1.22)
Felt unhappy	33,329 / 9		1.11 (1.04–1.18)	1.09 (1.03–1.17)	1.10 (1.02–1.18)	1.05 (0.97–1.13)	1.04 (0.96–1.12)
Did not enjoy life	33,329 / 9		1.10 (1.04–1.15)	1.08 (1.02–1.14)	1.08 (1.03–1.14)	1.03 (0.97–1.09)	1.02 (0.97–1.08)
Felt sad	26,528 / 7		1.07 (1.01–1.12)	1.05 (1.01–1.10)	1.05 (1.01–1.10)	0.99 (0.94–1.05)	1.00 (0.95–1.04)
Talked less than usual	9,786 / 3		1.06 (0.99–1.15)	1.05 (0.98–1.14)	1.06 (0.98–1.15)	1.00 (0.92–1.09)	1.00 (0.92–1.09)
Felt worse than others	9,786 / 3		1.05 (0.97–1.13)	1.02 (0.96–1.10)	1.05 (0.96–1.15)	1.03 (0.95–1.12)	1.02 (0.95–1.10)
Bothered by things	9,786 / 3		1.05 (0.94–1.16)	1.04 (0.95–1.15)	1.05 (0.95–1.16)	0.96 (0.85–1.09)	0.96 (0.86–1.08)
Felt hopeless about the future	10,972 / 4		1.04 (0.97–1.11)	1.02 (0.95–1.10)	1.04 (0.98–1.10)	1.00 (0.92–1.09)	1.00 (0.92–1.09)
Felt fearful	9,786 / 3		1.03 (0.87–1.23)	1.03 (0.86–1.22)	1.02 (0.84–1.25)	0.97 (0.77–1.22)	0.97 (0.76–1.23)
		0.8 1.0 1.5					

(adopted from Frank P et al. Am J Psychiat 178(12), 1107–1118, 2021)

a. Model 1 was adjusted for age and sex. Model 2 was adjusted as in model 1 with additional adjustment for education. Model 3 was adjusted as in model 1 with additional adjustment for health-related factors. Model 4 was adjusted as in model 1 with additional adjustment for behavioral factors. Model 5 was adjusted for all of the above-listed covariates.
b. Statistical significance after all adjustments.

toms. Many old-school psychopathologists would argue that psychiatric symptoms, behavioral abnormalities, autonomic symptoms, and somatic symptoms should not be treated at the same level in major depression, and that more emphasis should be placed on psychiatric symptoms. The DSM-5 diagnostic criteria for major depression may have placed too much emphasis on somatic symptoms in an attempt to create manipulative criteria to increase diagnostic concordance.

5. Sickness behavior induced by cytokines

Many people experience physical illness after viral or bacterial infections. They become febrile, feel nauseous, and lose interest in the outside world/environment. Easy fatigue, poor sleep, low mood, irritability, and decreased attention and memory are common. The core effects of peripheral inflammation from such infections did not attain enough attention from the viewpoint of depressive disorders. Inflammation caused by peripheral infections produces inflammatory cytokines, which may act on the brain to induce sickness behavior. Persistent immune signaling via elevated cytokines at the site of infection in systemic infections, cancer, and autoimmune diseases may exacerbate pathological reactions and may induce depression, if further developed. In this sense, inflammation may be a biological factor that increases the risk of depression rather than a psychosocial factor.

The pathological response to cytokine hyperactivity is a normal endocrine, autonomic nervous system, and behavioral response to infection. The production of inflammatory cytokines (interleukin-1α and β [IL-1α and IL-1β], tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6)) at the site of infection triggers a pathological response. However, inflammatory cytokines have been shown to induce not only pathological reactions, but also major depression, suggesting that the brain-cytokine system is greatly involved in human behavioral patterns, including major depression.

Cytokine-induced pathological responses and symptoms of major depressive disorder have many

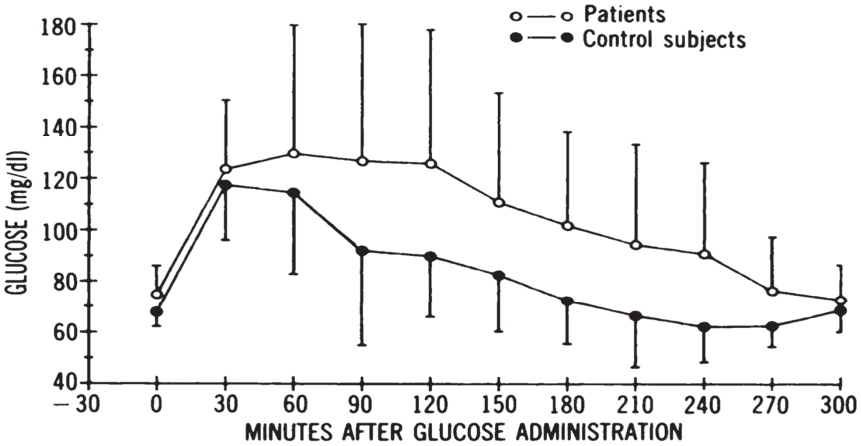
things in common, including withdrawal from the outside world, physical pain, fatigue, and indifference to rewards. The indifference to rewards seen in laboratory animals is reminiscent of anhedonia, a feature of human depression. The decrease in sweet-taste preference and exploratory movements seen as pathological responses in laboratory animals is known to be alleviated by antidepressant treatment. It is widely known that approximately one third of IFNα-treated patients have major depression. Also, major depression is more likely to occur in patients with chronic inflammatory diseases, such as cardiovascular disease, type 2 diabetes, and rheumatoid arthritis. Although there is partial overlap between morbid response and major depression, morbid response is an adaptive response to infection that resolves when the source of infection is eliminated. Major depressive disorder may be considered a pathological adaptation to a pathological response to infection (Dantzer, 2008).

6. Insulin resistance (IR) and depression

The prevalence of depression in patients with diabetes mellitus is reportedly approximately 15%, about three times higher than the prevalence of depression in the general population, suggesting that patients with diabetes mellitus are more likely to develop depression. Such patients are more likely to have elevated blood glucose levels with worsening depression, 57% of patients who receive electroconvulsive therapy (ECT) have improved diabetic symptoms, and depressed patients with diabetes mellitus have improved hyperglycemia with ECT, but poor response to insulin tolerance tests and decreased glucose use in glucose tolerance tests (GTTs).

Insulin resistance in depressed patients was recognized from early times. In 1988, Winokur et al. performed a 5-hour oral glucose tolerance test (GTT) in 28 depressed patients and 21 healthy subjects to measure serum glucose and serum insulin and serum glucagon levels. Depressed patients had baseline hyperglycemia, large blood glucose increases and large insulin secretion from the GTT test, but glucagon levels remained unchanged. These results suggest insulin resistance in depressed patients (Winokur, 1988) (Figure 1).

A meta-analysis of the prevalence and odds ratios of major depression in adults with type 1 and type 2 diabetes mellitus was reported (Anderson, 2001). The report examined the complication rate of major depression in the diabetic group for 42 articles picked up through database searches. The incidence of major depression was twice as high in the diabetic group as in the non-diabetic group (OR= 2.0, 95% CI 1.8 -2.2) and was significantly higher in the diabetic group than in the non-diabetic group, depending on gender, diabetes type (I/II), location of subjects (clinic/region), and diabetes assessment method (questionnaire/diagnosis). The prevalence of complicated major depression was higher in women (28%) than in men (18%), higher in the uncontrolled group (30%) than in the controlled group (21%), higher in the clinic group (32%) than in the community group (20%), and higher in the questionnaire group (31%) than in the standard diagnosis group (11%). This all suggests an



(adopted from Winokur A et al. Am J Psychiat 145(3),325-330, 1988)

Figure 1. Mean+-SD glucose responses after oral glucose tolerance test in 28 patients with depression and 21 healthy control subjects.
*Patients had greater cumulative glucose levels over time (Welch's T=3.11. df=38, p=0.004), and there was a significant group by time interaction effect (F=3.21, df=10.470, p=0.02 after Greenhouse-Giesser adjustment). The repeated measures test for a difference in the overall glucose level yielded F=10.25, df=1.47, p=0.002.

association between diabetes mellitus and higher risk of depression. Diabetes doubles the risk of complication of depression (Anderson, 2001), but the following two scenarios are possible: major depression may be induced as a consequence of diabetes, or major depression may be a risk for diabetes.

Regarding the causal relationship between diabetes and depression over time, Pan et al. conducted a ten-year prospective observational study because a 60% increased risk of type II diabetes mellitus had previously been reported to correlate with a 60% increased risk of type II diabetes mellitus in patients with major depression (Pan, 2010). Of 65,381 women (aged 50-75 years), 2,844 (4.3%) developed type II diabetes, compared with those with Mental Health Index (MHI-5) scores of 80-100, those with MHI-5 scores of 76-85 and 53-75, and major depression had an increased risk of developing type II diabetes, in that order. In addition, 7,415 people had major depression, and compared with the non-diabetic group, the risk of developing major depression was 1.29 in the diabetic group, 1.25 in the non-diabetic group, 1.24 in the diabetic drug use group, and 1.53 in the insulin treatment group, indicating that the correlation between diabetes and major depression is bidirectional.

Recently, the results of a cohort study of Dutch people (The Netherlands Study of Depression and Anxiety [NESDA]) were published (Watson, 2021). The study focused on triglyceride (TG)/high-density lipoprotein (HDL) ratio, fasting blood glucose, and abdominal circumference as surrogate markers of insulin resistance at baseline, and used these indicators to ascertain whether surrogate markers at 2 years would predict the development of major depression during the subsequent 9-year observation period. In a prospective study of 601 individuals (18-65 years) with no history of depression or anxiety disorders at baseline, 14% developed major depression during the 9-year study period. When risk was assessed for each surrogate marker, the hazard ratio for high TG/HDL ratio was 1.89, high fasting blood sugar level was 1.37, and large abdominal circumference was 1.11. All surrogate markers were positively associated with the development of major depression. Two years later, fasting blood sugar (prediabetes stage) was positively associated with the development of major depression (hazard ratio 2.66), but TG/HDL ratio and abdominal circumference showed no correlation. These results indicate that these three surrogate markers may reflect insulin resistance and correlate with the future development of major depression, suggesting that insulin resistance and metabolic abnormalities may lead to the development of major depression (Watson, 2021).

7. Behavioral changes in insulin receptor-deficient animals

As discussed above, many reports have suggested the relationship between diabetes and depression, but the mechanism behind diabetic induction of depression is unclear. Insulin resistance may be related to inflammation and cytokine production in the brain under internal stress, and the relationship between depression and diabetes could be a consequence of abnormalities in insulin regulation and monoamine metabolism due to abnormal mitochondrial function.

Kleinriddersa et al. created NIRKO mice, which are deficient in insulin receptors (IR) in the brain, by crossing IRlox/lox mice with Nestin-Cre transgenic mice. Insulin signaling and interesting behavioral abnormalities in NIRKO mice were reported (Kleinriddersa, 2015), which may explain one of the mechanisms of insulin resistance leading to major depression.

In NIRKO mice, IR mRNA in the brain is reduced by 95%, with regional IR mRNA reductions as well as insulin receptor protein reduction in the hypothalamus, hippocampus, prefrontal cortex, striatum, nucleus accumbens, and ventral tegmental area. NIRKO mice do not show behavioral abnormalities in their youth, but at 17 months of age, they begin to exhibit anxiety and depression-like behavior, indicating that animals with a specific insulin receptor deficiency in the brain develop depression-like behavior and anxiety symptoms in later life as a result of duration of insulin resistance. In these animals, mitochondrial function in neurons in the dorsal striatum and nucleus accumbens is reduced, oxidative stress is increased, and there is elevation of dopamine-metabolizing enzymes, monoamine oxidase MAO-A and MAO-B activity. Insulin resistance may therefore be a possible mechanism for the development of depressive symptoms in insulin receptor-deficient mice, as insulin signaling in the brain is attenuated, resulting in mitochondrial dysfunction and increased oxidative stress. In an experimental system using cultured cells, decreased insulin signaling has been confirmed to upregulate MAO-A and MAO-B expression, inferring that decreased insulin signaling increases dopamine turnover and decreases dopamine levels.

Insulin receptor-deficient animals do not show behavioral changes in their youth, but as they age, they exhibit behaviors that resemble anxiety and depressive symptoms. These behavioral changes are sec-

ondary to decreased dopaminergic signaling in the striatum and nucleus accumbens, which increases dopamine metabolic turnover, MAO A and B activity enhancement. Central insulin resistance can therefore be considered to elicit dopamine metabolism and age-related behavioral changes, directly linking the onset of depression due to insulin resistance to the onset of type 2 diabetes.

8. What is currently known about major depression?

Both major depression and diabetes mellitus are currently gradually on the rise. In the United States, diabetes mellitus affects 23.5 million people, or 10% of the population, with a prevalence of 23% among those over age 60. Meanwhile, 14.8 million people, or 6.7% of the population, have major depression, and the lifetime prevalence of major depression is reportedly significantly higher among women (20%) than men (12%). (McIntyre, 2021).

As mentioned above, there are numerous cross-sectional studies have shown correlation between abnormal glucose metabolism, type 2 diabetes mellitus, obesity, and metabolic syndrome and depression (Wang, 2019). Cross-sectional studies have also suggested that depression may be mediated by inflammation, oxidative stress, and other factors (Nemeroff, 2020). The previously mentioned study by Watson et al. showed the association through a longitudinal study.

In animal studies, insulin resistance correlates with depressed behavior and cognitive function (Reagan, 2021). Insulin is also known to act on neurotransmitters such as dopamine (Kullmann, 2021). It is also involved in neuroplasticity, neuronal differentiation, and long-term potentiation (LTP) (Yao, 2018). Functional brain imaging has also shown that insulin signaling is involved in resting-state connectivity (Cui, 2021). Half a century of clinical research on major depression has produced some results, but still not enough. According to a recent review article, the current challenges can be summarized as below (Nemeroff, 2020).

Firstly, the diagnostic problem of major depressive disorder remains unresolved because of the great heterogeneity implied by the diagnosis of major depression. The definitions of responsiveness and remission are arbitrary and their usefulness remains problematic. Although HAM-D scores of 7 and MADRS scores of 10 are used as indicators of remission, it is unclear whether they truly indicate remission of major depression. Similarly, no generally accepted consensus has been reached on the definition of treatment resistance, and it remains unclear how comorbidities with major depression, such as PTSD, OCD, social anxiety disorder, and generalized anxiety disorder, should be treated in clinical research or practice.

A second challenge is that it is clear that one therapy will only result in remission in a subset of patients with major depression. Current therapies are therefore suboptimal for many and probably inadequate for most patients. Various augmentation therapies, even if effective for some patients, have many side effects (e.g., atypical antipsychotics, lithium).

Thirdly, the mechanism behind the action of antidepressants remains unknown. Despite half a century of research in this area, there is no established theory of antidepressant action especially with applicability to all antidepressants. The mechanisms of antidepressant action may involve monoamine circuits, neurogenesis, second messengers, or changes in gene expression, but the mechanisms of action of ECT, TMS, VNS, and psychotherapy remain unresolved. The mechanism behind action of potentiation therapy is also unclear.

Moreover, the goal for personalized medicine or treatment for major depression, which is to screen out those at risk and to provide the best and safest treatment, has not yet been achieved.

Finally, much of this inadequate status quo is due to our poor understanding of the pathophysiology of major depression. Despite many years of research, the basic causes of major depression remain unknown, although a “window” into the brain has been opened. Considerable progress has been made in genomics, epigenetics, inflammation, and environmental factors. Perhaps major depression is the last common pathway to be reached via multiple pathways. As examples, major depression due to hypothyroidism and major depression due to hypogonadism clearly have a neoplastic basis and differ from major depression that develops from stress as a primary cause. Why major depression is more common in women than in men remains unclear. Mechanistic studies explaining the high comorbidity of major depression and physical illness are lacking and somatic causes of major depression have not been sufficiently studied.

9. Diversity of major depression

As pointed out by many experts including C.B. Nemeroff, the concept of major depression is not yet well organized, and a wide range of conditions including inflammation, insulin resistance as well as psychosocial factors are thought to eventually cause major depression. Comprehensive discussion of all

possible conditions leading to the final common pathway of depression phenotype is very difficult, so this article will touch on just two aspects which indicate the main reasons for the diversity of major depression: time dimension of symptom sequence of major depression, and the interaction between physical and psychogenic factors in elderly people.

9-1. Timeline of onset of symptoms

Onset of symptoms of major depression usually follows a typical time course in the majority of patients. Depression begins with a depressed mood, followed by pessimistic thoughts, followed by restrained speech and behavior, and finally by autonomic nerve and physical symptoms. When depression goes into remission, the order of the reduction of symptoms is the opposite of that of the onset: physical symptoms, autonomic nerve symptoms are resolved followed by conversation and behavior, and then by pessimistic thoughts improve in that order, and the depressed mood tends to persist until the end. During the extreme phase of a depressive episode, when the behavior itself is suppressed, even if there are suicidal thoughts due to depressed mood and pessimistic thinking, suicidal behavior is less likely to occur because the behavior is less likely to be acted upon. Rather, the risk of suicide is higher at the beginning of the depressive episode, when behavioral restraints are no longer in place, and during recovery from the depressive episode.

The DSM-5 concept of major depression does not take into account any such changes in symptoms over time. At the time of diagnosis, a diagnosis of major depression is made if five or more of the nine operative diagnostic criteria are met. The nine diagnostic criteria include consideration of mood, thinking, speaking, behavior, autonomic symptoms and somatic symptoms. This is one of the reasons that the diagnosis of major depression includes both psychogenic and psychosomatic causes of depression, and it allows for hybridization in the diagnosis of major depression (Figure 2).

9-2. Somatic and psychogenic causes of depression in elderly people

About 15% of people over 65 years of age are in a state of minor depression, and the prevalence of major depression (MDD) is estimated to be 6% on average, but many types of depression in elderly people are not accompanied by the typical symptoms described above. Many types of depression characteristic of elderly people are atypical, such as agitation and anxiety (agitated depression), physical complaints (masked depression), depression that is difficult to distinguish from dementia (pseudodementia), and delusion (Cotard's syndrome in extreme cases). The characteristics of depression in elderly people can be summarized as commonality of physical complications, environmental and psychological factors having a large influence, atypical pathophysiology, and common side effects of medications.

The reason for depression being common among elderly people is thought to be the involvement of both physical and psychosocial factors. Post-stroke depression has long been the focus of attention as a representative of physical factors. According to Robinson & Price, who proposed the concept of post-stroke depression, 19.3% of elderly post-stroke

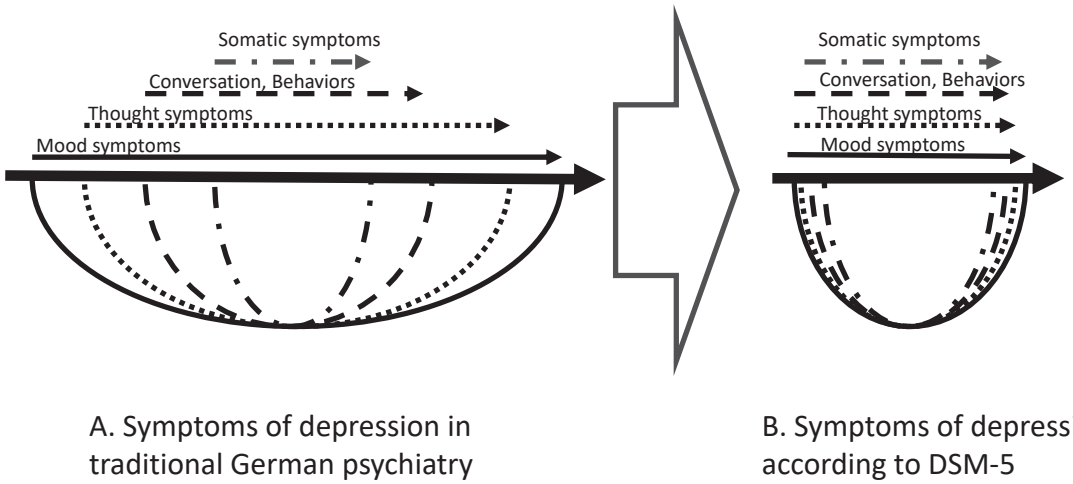


Figure 2. Difference in timeline of symptom onset in traditional psychiatry and modern psychiatry based on DSM-5
In traditional psychiatry, sequential onset of symptoms is seen in typical cases with depression. Depressed mood, pessimistic thoughts, restrained speech and behavior, and autonomic nerve and physical symptoms appear in this order. When depression remits, symptoms are reduced in the opposite order. The DSM-5 concept of major depression does not take into account any such changes in symptoms over time.

patients reported major depression and 18.5% minor depression (Robinson, 1982). The symptoms of post stroke depression cannot be distinguished from those of major depression, and the stroke sites most likely to cause depression are cortical and subcortical infarcts in the left hemisphere. About 60% of infarcts are in the left frontal lobe, and depressive symptoms are reported to be stronger in the left frontal lobe when the infarct is closer to the frontal pole.

Depression has been shown to be more common in patients after a stroke than in orthopedic patients with a similar degree of behavioral restriction (Folstein, 1977). Depression is more common in stroke and carotid artery stenosis than in peripheral vascular disease (Rao, 2001), and the frequency of depression is similar in stroke and myocardial infarction (Aben, 2003). Vascular depression caused by systemic vascular factors has been suggested (Alexopoulos, 1997; Krishnan, 1995). White matter lesions and deep gray matter (basal ganglia) lesions are often observed in depression in old age, and small infarcts in the cerebrum, including asymptomatic ones, can induce depression. This has led to the view that vascular depression is a common cerebrovascular disorder in elderly patients.

Conversely, it has been noted that psychosocial factors are often involved in depression in elderly people. Elderly people have often experienced numerous kinds of losses: psychosocial factors that may cause depression in the elderly include the decline of physical functions due to aging (loss of health), loss of previous social roles due to retirement or independence of children (loss of role), loss of income due to loss of job (economic loss), and death of spouse, family, friends, and acquaintances (loss of companionship).

10. Toward the integration of physical and psychogenic factors

Human mood fluctuates within a certain range. The upper part of the Figure 2 shows the mood change of a healthy person, and any person will show a wave of a certain width in response to events in his or her life. A case in which such a person exhibits depression by combining three factors: the baseline level of mood (L), the amplitude of the mood wave (A), and the socially acceptable width of the mood (W) is described here (Figure 3).

Assuming that depression occurs when the lower part of the mood wave falls through the tolerance range, we can consider three types of depression: when the tolerance range narrows (type 1), when the amplitude of the mood wave increases (type 2), and when the level at which the mood wave is located in a lowered position despite the amplitude of the mood wave being unchanged (type 3). These will be referred to as tolerance abnormality (W), amplitude abnormality (A), and reference position abnormality (L), the three basic types, but because there may be cases in which two or even all three factors are abnormal, theoretically, seven types can be distinguished: W, A, L, LW, AW, AL, and ALW. This exemplifies the diversity of major depression (Figure 4).

Type 1 describes a case in which a person who was not considered to have depression in the past may present with depression due to a narrowing of social tolerance, and may explain depression due to social factors. Type 2 is a case in which the amplitude of the mood wave increases and penetrates downward beyond tolerance, which is easily predicted from the increase in depressed mood when exposed to psychological stresses such as bereavement, divorce, accident, or unemployment. Depression can also be caused by a decrease in the level of the average normal mood baseline, even though the amplitude of the mood waves may be similar to that of healthy individuals. Depression associated with hypothyroidism could be explained by such a decrease in the mood baseline. Such conditions may be closely related to physical factors, such as inflammation and insulin resistance.

In this way, we may be able to understand the diversity of depression and the mechanism by which the combination of psychological, physical, and social factors can elicit diverse depression.

Experience of childhood stress may be considered as a link between psychogenic and somatic factors. Recent advances in our understanding of developmental disorders and the development of brain functions and networks have led to an examination of the effects of childhood psychological stress in many psychiatric disorders. Psychological stress, including childhood abuse, could for example cause adverse effects on insulin signaling. Insulin resistance could be a surrogate marker for social or environmental stressors. Longitudinal studies utilizing various functional brain imaging studies may provide useful insights into these aspects.

As a specific intervention, lifestyle modification incorporating exercise is expected to improve insulin resistance; promoting exercise to the general population as primary or zero-primary prevention measure may have the potential to prevent depression by improving insulin resistance (Harvey, 2018). As these

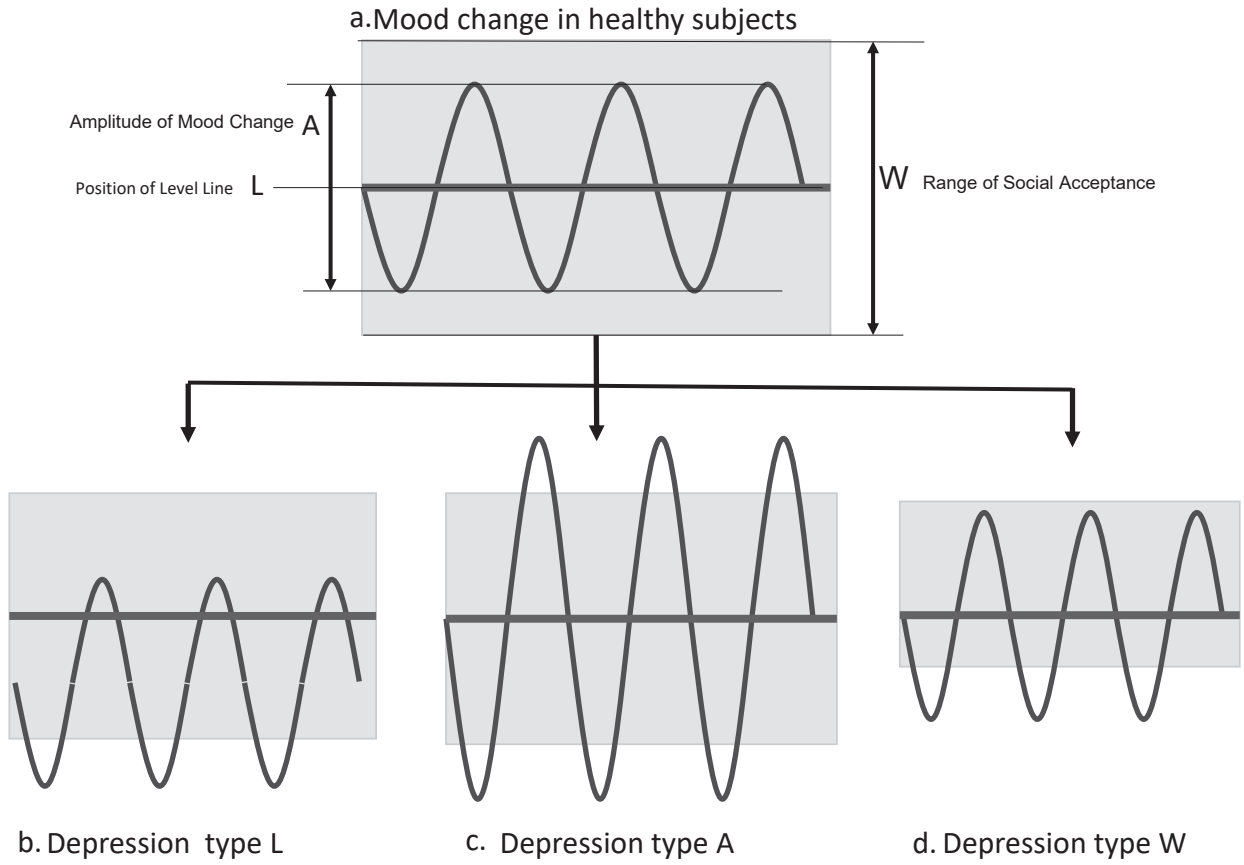


Figure 3. Three basic subtypes of depression
a. Mood change is observed in healthy subjects, with the amplitude (A), positioned on the neutral level line (L), which is within the range accepted by social norm (W).
b. Scheme of depression type L, in which the amplitude of mood change is the same as healthy subjects, but the positioning of the mood change base line is lowered so that the lower peak of mood change exceeds the limit of social allowance.
c. Scheme of depression type A, in which the amplitude of mood change is larger than that of healthy subjects. Even though the positioning of the mood change is the same with that of healthy subjects, the lower peak of the mood change exceeds the limit of social allowance.
d. Scheme of depression type W, in which the positioning and amplitude of mood change is the same as those of healthy subjects. Due to the narrowing of the social allowance, an individual with the similar mood change is diagnosed with depression.

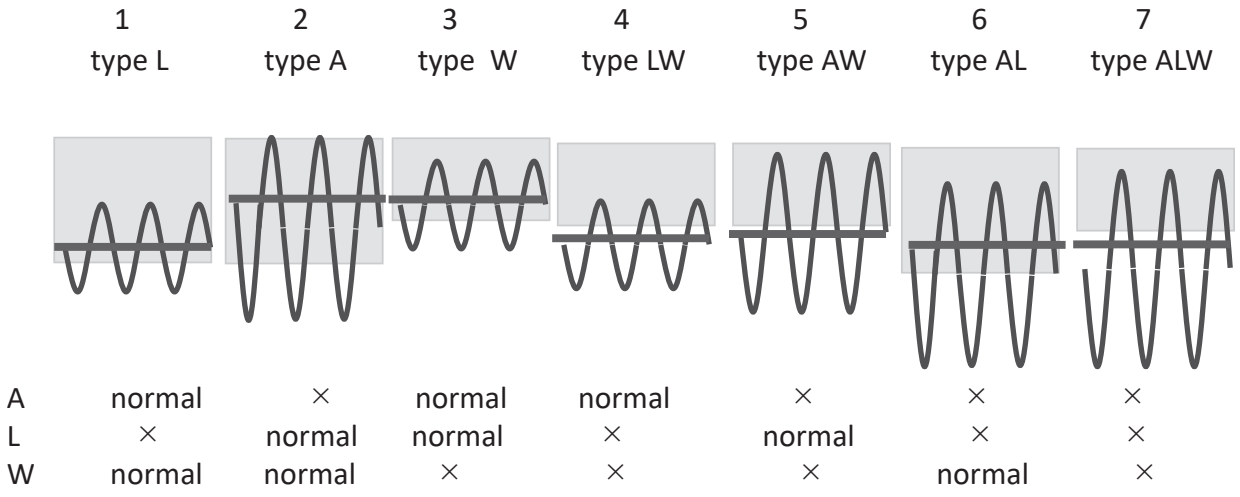


Figure 4. Seven possible subtypes of depression
Depression may occur by the combination of three factors, L, A, and W. L = lowered position of mood level line. A = increased amplitude of mood change. W = narrowed width of social allowance. Seven subtypes of depression are theoretically possible, three basic subtypes (type L, A, and W) and four combined subtypes with two factors involved (AW, LW, and AL) and three factors (ALW).

findings accumulate, improving insulin resistance with medication before the onset of illness may also be a possible way to alleviate depression. An integrated understanding of the physical and psychogenic causes of depression may point the way toward prevention and treatment of depression.

CONCLUSION

Major depression disorder (MDD) has been and the main target disorder of psychiatry in many years. In the DSM diagnostic system, MDD is diagnosed with 5 or more out of 9 diagnostic criteria, in which physical symptoms and mental symptoms are evenly listed, Simply looking at the diagnostic criteria, it is difficult to judge whether MDD should be understood as a mental disease or as a physical disease.

On the other hand, with the development of biological research on depression, more and more new biological findings have been reported, some of which clearly indicate that depression is induced not only by psychosocial factors but also by systemic inflammation and insulin resistance.

The authors discussed how we should understand depression, which has been greatly expanded by the introduction of an operational diagnostic system. Based on the idea that depression develops as a result of a combination of physical, psychological, and social factors, the author proposes the three prototypes of depression; (type A) the range of mood swings expands, (L-type) mood fluctuations level is lowered while the range of mood swings does not change, and (W-type) the range of mood fluctuations dose not change, and the level is not lowered, but the range of social tolerance is narrowed.

Furthermore, in actual depression, in addition to the basic form, there are cases with two overlapping factors (AL, AW, LW) and those with three factors overlapping (ALW). Under this model, there are deven subtypes of depression. In this model, we can explain the mechanism of various types of depression.

Conflicts of Interest: None

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