Depression: An Insight and Need for Personalized Psychological Stress Monitoring and Management

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The modern lifestyle, environment and social structures of communities have led to significant increase in the psychological and oxidative stress levels of people, which is clearly evident in terms of social misbehaviour somethimes escalating to growing aggressiveness, uncontrolled violence and misconduct. These behavioral changes not only affect public but also the families. The chronic psychological stress leads to depression, which is apparent in the form of persistent sadness, lowered mood, low energy level, loss of interest or pleasure, feelings of guilt, disturbed sleep, anhedonia, low self-esteem and self-confidence, loss of appetite, low libido, poor concentration, and difficulty in functioning normally. Depression has been recognized as a hidden burden by the World Health Organization (WHO) in 2013 [1], which is an exponentially growing global epidemic and the leading cause of disability worldwide (Table **1**). There are at least 350 million people living with depression, while more than 450 million suffer from the mental disorders mainly due to prolonged psychological stress. These numbers are critically high as the incidence of depression stands at nearly the same level as diabetes that accounts for 382 million diabetics [2]. Moreover, it not only affects the person with depression, but also significantly impacts the mental health of their loved ones and the society due to difficulties in managing relationships and social contacts. It carries a huge burden in terms of treatment costs, effect on families and carers, and loss of workplace productivity. Depression accounts for ~12% total years lived with disability [3] in an affected individual, which is a tremendous loss of work productivity. It has been firmly established that depression affects women more commonly than men. The burden of depression is 50% higher for females than males [4]. The percent of total years lost due to disability (YLD) in males and females in 2004 were 8.3 and 13.4, respectively.

The extreme form of depression leads to suicide, as evident from about 1 million people that commit suicide each year, while 20 million or more make an attempt. Despite the availability of effective treatments, most people with depression do not receive the healthcare and support due to lack of access to treatment and the lingering social stigma attached to mental disorders. The economic burden of mental disorders over the next 20 years has been estimated to be €11,495 billion [1]. However, despite the percentage of global burden of disease due to mental disorders being 13%, the percentage of healthcare budget for mental health is only 3%. The European Brain Council have mentioned 2014 as the *"Year of the Brain in Europe"* in order to raise awareness and educate people on brain disorders [5].

The most severe form of stress related depression are observed in patients with post-traumatic stress disorders following sexual assault, major tissue injury and sepsis, war veterans and the experience of other kinds of disasters. This context is of critical importance as a major primary insult, which may be a psychological hit or physical injury followed by a prolonged misbehaviour or stress, conditions the manifestation of mental disorders and leads to depression. Stress can also affect the next generation as the epigenetic mechanisms shape short- and long-term responses to stress [6]. WHO has started the Mental Health Gap Action Programme (mhGAP) [7], which aims at creating options for the management and treatment of people with depression. This alarming

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Table 1: WHO Estimates of ten Leading Causes of Burden of Disease, World, 2004 and 2030 [4]. DALYs is Disability-Associated Life Years

2004 Disease or injury	As % of total DALYs	Rank	Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1	**1**	**6.2**	**Unipolar depressive disorders**
Diarrhoeal diseases	4.8	2	2	5.5	Ischaemic heart disease
Unipolar depressive disorders	**4.3**	**3**	3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4	4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5	5	3.8	COPD
Cerebrovascular disease	3.1	6	6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7	7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8	8	2.7	Refractive errors
Road traffic accidents	2.7	9	9	2.5	HIV/AIDS
Neonatal infections and other	2.7	10	10	2.3	Diabetes mellitus
COPD	2.0	13	11	1.9	Neonatal infections and other
Refractive errors	1.8	14	12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15	15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19	18	1.6	Diarrhoeal diseases

incidence of depression worldwide is a wakeup call to find solutions to address this rapidly growing global epidemic. Moreover, it is now a well-established fact that most of the diabetics have co-existing depression, which is associated with significantly increased morbidity, mortality and healthcare cost [8] (Figure **1**). Therefore, the expected increase in the number of diabetics from 383 million in 2013 to 592 million in 2035 [2], will also lead to substantial increase in the number of diabetics with co-existing depression. Depression is associated with a 60% increase of type 2 diabetes [9]. Moreover, patients with diabetes and coexisting depression had 4.1-fold increase odds of disability compared with 1.7-fold increase among adults with diabetes only and 1.3-fold increase among adults with depression alone [10]. Depression significantly deteriorates the quality of life of diabetics [11] and increases the all-cause mortality. It has been found that patients with diabetes and depression had higher diabetes-related medical costs (€ 2368) than patients with diabetes alone (€ 683) [12]. A study showed that the total healthcare expenditures were 4.5 times greater among diabetics who were depressed than those who were not depressed [13]. The practice guidelines from International Diabetes Federation (IDF) clearly indicate that as diabetics are more likely affected by depression, there is a strong requirement of periodic assessment and monitoring of depression and other mental health conditions for more effective diabetes management [14].

There is an immense need for an innovative healthcare monitoring and management system for the effective management of psychological stress and, more importantly, for timely interventions. The previous attempts to identify a single biomarker for psychological stress analysis have been unsuccessful due to the multi-factorial nature of psychological stress, where environmental, genetic and psychosocial factors also

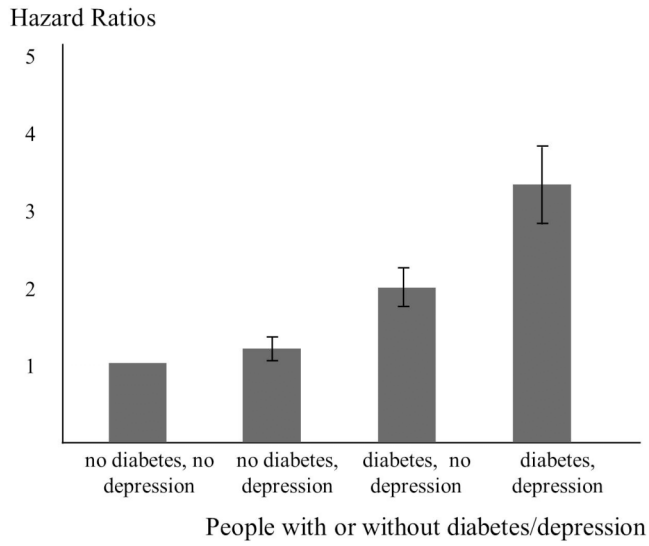

Figure 1: Effect of depression on all-cause mortality in patients with diabetes [8]. Reproduced with permission from Elsevier Ireland Ltd.

play a prominent role. The psychological stress can be monitored by the determination of diurnal cortisol concentrations, a neurobiological stress hormone that reflects the hypothalamic–pituitary–adrenal (HPA) axis activity. However, it has become firmly established from the advances in the field during the last decade that several other biomarkers are causally related to cortisol kinetics and impaired HPA axis and body response. Such inflammatory biomarkers should also be considered for the more effective determination of psychological stress levels and its management. The early-stage diagnosis of psychological stress can provide the desired opportunity to prevent or delay the onset of depression. It has been stated that 60-80% of persons afflicted with depression can be treated by anti-depressants and structured physiological therapies, but fewer than 25% of these are actually receiving such treatments due to the lack of early-stage stress monitoring procedures [15]. This is due to the lack of skillset of physicians in the primary care settings, who are rarely trained to distinguish depression from other medical conditions that have the same symptoms [16].

In medicine, “stress” is defined by the body’s non-specific response to an any extra demand by physical, psychological or pharmacological events. It induces activation of the HPA axis that acts on the adrenal glands to release cortisol. The continuous stress results in the stimulation of glucocorticoid receptors in the hippocampus that activates the hypothalamus, which secretes the corticotropin-releasing hormone (CRH). Subsequently, the CRH activates the pituitary gland to release adrenocorticotropic hormone (ACTH) into the bloodstream, which then activates the adrenal glands to secrete cortisol. This process creates a negative feedback loop, where the excess cortisol activates the brain's glucocorticoid receptors, thereby suppressing the production of CRH. However, this loop is non-functional in depressed patients, thereby resulting in excess production of CRH and cortisol. The chronic elevation of cortisol increases blood sugar, blood pressure and protein catabolism apart from the suppression of immune cells, insomnia, and suppression of gastrointestinal function and digestion. This prolonged elevation of cortisol may lead to diabetes and hypothyroidism. The chronically activated cortisol increases the 5-HT2A (5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled) receptors in the cerebral cortex of brain and reduces the 5-HT1A receptors in hippocampus. The prolonged stimulation of the HPA axis results in the neuronal loss in CA3 region of hippocampus, which may lead to a number of cognitive dysfunction disorders including the inability to experience pleasure [17]. In contrast, the normal cortisol level is essential in protecting humans from the stress mediated by inflammatory cytokines that are released by activated macrophages. The specific areas in brain are highly sensitive to inflammatory cytokines due to microglial activation and the negative effect on oligodendrocytes and myelination. The initial phase of stress is characterized by high levels of inflammatory cytokines and low levels of α-amylase, while the second phase of mental illness is characterized by a high cortisol level and a unique loss of cortisol peaks in the morning and low cortisol concentrations in the evening hours [18]. Many seriously depressed patients have high blood levels of cortisol due to chronic stress. However, in the absence of high cortisol, minor stressors can become major burdens. A missed meal can turn into a hypoglycemic episode due to the absence of cortisol that raises the blood sugar. Also a minor allergy can turn into asthma. When the adrenals can't respond to stress, the body starts deteriorating. The greater is the incidence of this loss of response by the adrenals, the more is the stress experienced by depressed persons. The vicious cycle [18] of stress-induced effects on cortisol levels is shown in Figure **2**. The inflammatory cytokines represent the major effectors of stress to the brain and the consequence of HPA axis activation and cortisol response to combat inflammation (Figure **3**).

It is generally believed that brain and immune system communicate through cytokines, neuro-peptides, and neurotransmitters. Stress is believed to be the result of inflammation that stimulates innate

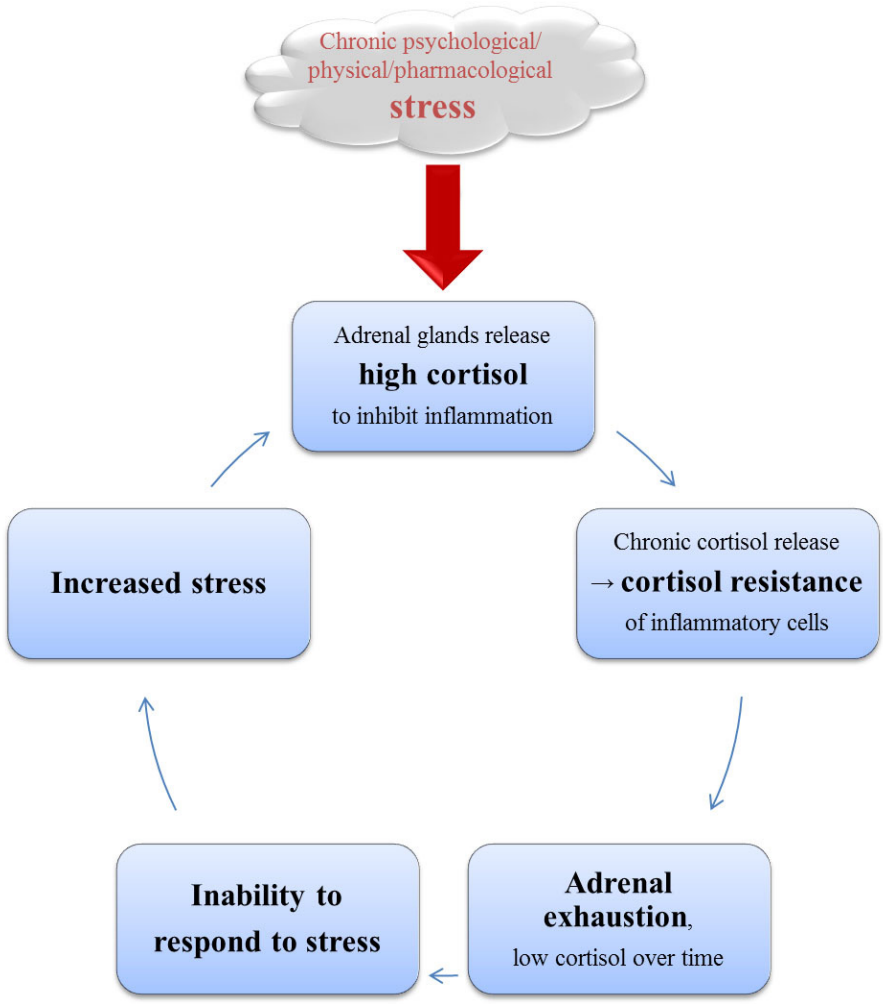

Figure 2: The vicious cycle of stress-induced effects on cortisol level.

immune cells such as macrophages and microglia to secrete inflammatory cytokines. The brain tries to combat this inflammation *via* increased cortisol secretion. The elevated cytokines further deteriorate the brain chemistry due to the increased tryptophan degradation through interferon-γ induced 2,3 indoleamine dioxygenase (IDO) activity [19]. The stress response acting *via* the Sympathetic Nervous System (SNS) induces elevated cytokines in peripheral tissues such as blood and saliva. SNS releases catecholamines, which stimulate α- and β-adrenergic receptors on macrophages and dendritic cells to activate nuclear factor (NF)-κB, an important transcription factor for the release of pro-inflammatory mediators. On the other hand, this inflammation may impair the release of functional molecules, such as α-amylase in saliva. Moreover, the up regulation of human lipocalin-2 (LCN2) is expected to be the most important biomarker to selectively address inflammation related to metabolic dysfunction [20]. Pro-inflammatory macrophages and dendritic cells express a variety of tool-like-receptors, which respond to molecular entities derived from tissue damage (Danger Associated Molecular Patterns, DAMPs) as much as from pathogens (Pathogen Associated Molecular Patterns, PAMPs). The nature of inflammatory cytokines released is an indicator of the relative contribution of DAMP vs. PAMP induced stress and brain dysfunction. The brain recognizes the elevated systemic cytokine levels and induces the HPA axis to increase cortisol secretion, which inhibits the NF-κB signalling. Inhibitory parasympathetic nervous system (PNS) activity and possibly feedback mechanisms within the SNS are also thought to be involved.

Mental health is an important economic factor. The successful recovery and growth of economies is dependent on the mental health of the population as the good mental health contributes to economic productivity and prosperity. A bottom-up cost-of-illness study conducted to determine the magnitude of impact of treating depression to full remission showed that the

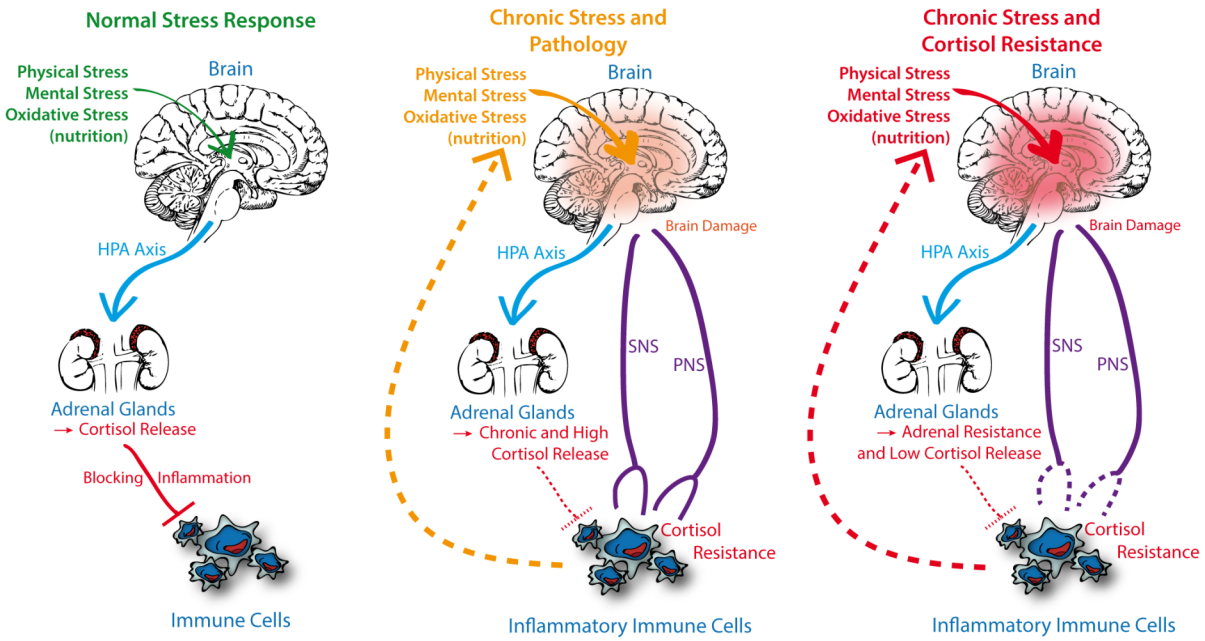

Figure 3: Role of stress induced activation of HPA axis, cortisol, and sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) neurotransmitter release to combat immune cell activation. Stress (green arrow acting on the brain) affects brain function dierctly *via* the Locus coeruleus in the brain stem, hypothalamus and other brain regions. In an healthy individual, this stress is compensated by cortisol (released *via* the HPA axis), which also blocks activation of inflammatory immune cells (left); Under chronic stress, cortisol is continuously activated but inflammatory immune cells downregulate their receptors and contribute to stressing brain regions by inflammatory cytokines (green dashed line). Inflammatory cells of hematopoietic system also affect human licocalin-2 (LCN2) production in the liver and α-amylase in saliva. When cortisol fails to downmodulate inflammatory cells, the state of stress is described as cortisol resistance (middle panel). In the most detrimental advanced stage of depression, adrenal resistance is the most important characteristic. In case of adrenal resistance, the adrenals attempt to help the body to resist prolonged stress by producing persistently increased cortisol. Subsequently, the ability of adrenal glands to make even normal amounts of cortisol is lost, which is known as adrenal exhaustion or adrenal fatigue. In this situation, the communication and regulatory function of the SNS and PNS is also affected, which may account for various aspects of immune dysfunction, such as increased and chronic infections or autoimmune diseases (right).

total annual per-patient cost for patients with major depression in remission was significantly lower than those on a depressive episode; € 8400 vs €13800 (in 2005) [21]. Remitting patients had significantly lower (up to 36%) direct health care costs and productivity losses compared with those who are not in remission. The greatest contributor to the burden of disease is productivity losses (indirect costs) [22]. The improved mental health in the workplace will lead to reduced employee sickness absence, better staff retention, and increased economic productivity and performance [23]. It will contribute to the policy objectives of EU's Lisbon strategy, which aims to make EU the most dynamic, competitive, sustainable knowledge-based economy, enjoying full employment and strengthened social and economic cohesion.

Most of the existing commercially-available *in vitro* diagnostic (IVD) kits, which are based on sandwich enzyme linked immunosorbent oassay (ELISA), detect only a single biomarker that cannot be relied upon to predict the psychological stress with high precision. Therefore, there is an identified market need for a personalised healthcare solution, similar to that of diabetic blood glucose monitoring [24-26], which will enable the effective determination of psychological stress, thereby providing the unique opportunity to effectively manage it *via* lifestyle or medical intervention. A variety of rapid and highly sensitive immunoassay formats have been developed recently for the detection of biomarkers [27-30]. Moreover, researchers have also started looking into point-of-care solutions, preferably involving the use of smartphones for personalized monitoring and management of diseases. Smartphones are ideal mobile healthcare devices that are omnipresent (~7 billion cellphone users covering 86% of population globally), continuously getting cheaper (€250 at present but estimated to drop to <€100 in the next four years for a standard smartphone), and have growing computational power and associated features, as desired for personalised healthcare monitoring [31]. It will enable the creation of a learning environment, where the end-users can analyze the IVD results and can act accordingly by lifestyle intervention, which will lead to visible and sustained health benefits. Therefore,

smartphone-based diagnostics will be unique in improving patient-centered approaches, where the patient will be an active decision maker in the care process. These developments in technology will pave the way for personalized psychological stress monitoring and management in near future.

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