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Review

Adiposity in depression or depression in adiposity? The role of immune-inflammatory-microbial overlap.

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Abstract: Metabolic disorders, metabolic syndrome and non-alcoholic fatty liver disease, and depression are those of the most common and debilitating disorders worldwide that often coexist further increasing mortality risks. Although the exact mechanisms underlying this association are poorly known, several hypotheses have been proposed: antipsychotic medication and antidepressants use, diet and physical activity or any other lifestyle factors. However, the high co-occurrence rate of depression and metabolic disorders suggests a possible pathophysiological overlap. In this paper I review several raised mechanisms for this overlap which are the hypothalamic-pituitary-adrenal axis dysregulation, immune alterations with chronic inflammation, as well as oxidative stress. In my view, there is one common thread running through all the aforementioned areas of pathophysiology which is microbiota alteration. So far, several possible interventions in our microbiota have been introduced into clinical practice - dietary and other lifestyle changes, supplementation with prebiotics or probiotics, fecal microbiota transplantation – but with vague indications. A better characterization of the above associations may represent a critical step at phenotyping, and a more targeted approach to the treatment of both depressive and metabolic disorders. At the end of the paper, I give several practical applications for future studies.

Keywords: depression, metabolic syndrome, non-alcoholic fatty liver disease, hypothalamic-pituitary-adrenal axis, inflammation, oxidative stress, microbiota

Metabolic disorders (MDs), metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD), and depression are those of the most common and debilitating disorders worldwide [1]. The one-year prevalence of depression is approximately 6% worldwide while the lifetime risk of depression (single or recurrent episode) is three times higher [2]. MetS, as a set of anthropometric, clinical and metabolic abnormalities (obesity, insulin resistance, dyslipidaemia and hypertension), has been defined different ways and some of the cut-off criteria vary considerably, thus making epidemiology studies difficult. However, the global prevalence is estimated to be about one quarter of the world population [3]. Moreover, depressive disorders (DDs) often coexist with MDs further increasing mortality risks [4,5].

A meta-analysis [6] showed that individuals with depression had 1.5 times higher odds of having MetS and prevalence of MetS in depressed subjects accounts for 30%. Moreover, very recent data from the Netherlands Study of Depression and Anxiety (NESDA) sample [7] did demonstrate that persons with atypical depression had significantly higher levels of inflammatory markers, BMI, waist circumference (WC) and triglycerides, or lower high-density lipoprotein cholesterol (HDL-C) than persons with melancholic depression. Additionally, in a large, nationally representative sample, it was

found that both obesity and MetS were associated with significant depressive symptoms independent of each other, and that participants with both conditions had the highest rate of depression as compared to the other groups [8]. Lately, it has been shown that individuals experiencing a current episode of major depressive disorder (MDD) are significantly more likely to have insulin resistance (IR) than non-depressed individuals [9]. The aforementioned liver equivalent of MetS, NAFLD, is characterized by excessive hepatic fat accumulation [10]. It is the most common cause of chronic liver disease in Western countries. Moreover, it is a multisystem disease. By analogy with MetS, a majority of deaths among IR and NAFLD patients are attributable to cardiovascular diseases (CVD) [11].

Although the exact mechanisms underlying this association are poorly known, several hypotheses have been proposed. First of all, antipsychotic medication use is associated with a significantly higher MetS prevalence. Moreover, augmentation with newer antipsychotics in non-elderly patients with depression was associated with increased mortality risk as compared to adding another antidepressant [12]. Use of antidepressants in general is uncertain [13]. Diet and physical activity accounted for 23% of the association between depression and the MetS [14]. The other factors coexisting in metabolic and depressive disorders remain poorly known. However, the high co-occurrence rate of DDs and MDs suggests a possible pathophysiological overlap. Although the precise mechanisms mediating the phenomenon have not yet been elucidated, the hypothalamic-pituitary-adrenal (HPA) axis dysregulation, immune alterations, inflammation, oxidative stress (OxS), autonomic nervous system dysregulation, IR or microbiome alterations are all interacting biological mechanisms that have been proposed [1,5,7,15–18]. It would be worth seeking for in-depth etiopathology overlap areas of the above syndromes to create new potential prophylactic or therapeutic methods. Research in this area may open door for establishing a subpopulation of patients sensitive to microbiota interventions.

To begin with, the common feature of affective and metabolic diseases is dysregulation of the HPA axis [19,20]. In depression, this axis is typically upregulated. The negative feedback of cortisol to the hypothalamus, pituitary and immune system is impaired. Excess release of cortisol into the circulatory system has a number of effects, including elevation of blood glucose, cortisol receptors desensitization leading to increased activity of the pro-inflammatory immune mediators and disturbances in neurotransmitter action [19]. However, it is worth noticing that atypical depression is associated with hypofunction rather than hyperfunction of the HPA axis, rather than a hyperfunction. In MDs, especially abdominal obesity phenotype and IR, mainly primary neuroendocrine dysregulation mechanisms are involved, as a result of genetic predisposition and altered coping with some environmental factors (stressors, lifestyle, nutrition) [20]. Final hypothalamic inflammation represents an interconnection between somatic diseases and DDs [21]. However, the exact pathophysiology of the dysregulation of the HPA axis in depression and MetS has not yet been revealed.

Inflammation in general as a response to a threat (injury/infection) is a highly beneficial process [22]. Nevertheless, a prolonged low-grade inflammatory response and systemic effects is a pathological feature [23]. It has been called chronic low-grade inflammation (CLGI) or metaflammation, and it is believed to originate, at least partially, from the abdominal adipose tissue representing a type of civilization disorder. Most modern chronic conditions may be associated with such a chronic inflammatory state which has been named Chronic Low-grade Inflammatory Phenotype (CLIP) [24]. Indeed, recent studies have confirmed that depression, anxiety and MDs are associated with CLGI. It is characterized by increased circulating pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (Il-6) levels, altered leukocyte population frequencies in the blood, accumulation of activated immune cells in tissues, including the brain [16,25]. Although far from conclusive, emerging evidence suggests that chronic inflammatory condition in the central and peripheral immune system may mediate a subset of DD [26]

commonly concurrent with obesity and metabolic diseases. This association is especially seen in atypical depression, where subjects show increased appetite along with symptoms of depression, which then correlate with elevated serum TNF-α and CRP [7]. Moreover, it was found that depressed patients with both obesity and MetS showed the highest levels of systemic inflammation measured by CRP [8]. However, the role of specific immune cells and cytokines in the relationship between MetS and depression still remains an open issue. Moreover, research evaluating effectiveness of interventions on metabolic and inflammatory pathways should include "immuno-metabolic" form of depression [15,18].

There is also a number of studies which demonstrate that OxS (a state of imbalance between the oxidative and anti-oxidative systems of the cells and tissues which leads to the damage of cellular macromolecules) along with inflammation pave the way for the development of metabolic [27,28] as well as depressive disorders [29–32]. It includes abnormal total antioxidant capacity (TAC), antioxidants, free radicals, oxidative damage and autoimmune response products. Additionally, poorer antidepressant treatment response was shown to be related to higher levels of OxS and antidepressant response was associated with a decrease in oxidative and inflammatory markers [31,32]. Importantly, elevated OxS in MetS promoting vascular inflammation has been shown to be a major risk factor for an increased risk of CVD [27].

Elucidating these mechanisms linking MetS, depression, the HPA axis, inflammation and OxS could generate new potential therapeutic targets or patient-specific strategies aimed at combating both metabolic and depressive disorders.

Recently, there has been much interest in the role of intestinal microbiota changes in the pathophysiology of civilization diseases. The term microbiota refers to trillions of organisms present in the human body that plays a crucial role in health, including the human immune status. The gastrointestinal (GI) tract contains the densest microbial community; however, its full diversity remains uncharacterized [33,34]. It should be underlined that microbiota in non-Westernized populations is still rich while diseases of the Western civilization are connected with depletion of our microbial community [35].

The GI microbiota has been shown to be an essential part of the bidirectional and complex gut-brain axis (GBA) [36,37]. Other pathways previously established include the autonomic and the enteric nervous systems, the neuroendocrine and the immune communication. The brain influences the motor, sensory, and secretory modalities of the GI tract, whereas, the gut influences brain function, especially in areas of the brain involved to stress regulation [38]. The connection between the gut and the brain may be proved by the comorbidity between GI and neuropsychiatric diseases[39–41]. The diversity of the gut microbiota has emerged to play a significant role in the occurrence of mood and anxiety disorders [42–45]. In recent studies gut microbiota taxonomical changes were associated with the severity of depressive symptoms in clinical population [46,47]. Reduced or absent Clostridia was consistently seen in those with depression, independent of the presence of anxiety. Conversely, reduced Bacteroides may be more associated with the presence of anxiety, independent of the presence of depression. These differences suggest that gut microbiota distribution could help clarify the underlying pathology of comorbid clinical presentation [48]. Additionally, an intestinal integrity and inflammation markers were associated with the response to treatment and severity of depressive symptoms [46]. However, little is known on how microbiota health is associated with specific features of DDs.

Moreover, there is scientific data on the implication of the intestinal microbiota function in the ethiopathogenesis of MetS and the connection of dysbiosis with abdominal obesity [49,50]. Taxonomically, the relative abundance of Firmicutes and Actinobacteria in obese individuals has been described and this obesity-associated gut microbiota is able to derive more energy from food and facilitate fat storage [51]. In addition, bacteria-derived products can induce adipose tissue inflammation [52]. Gut dysbiosis can also contribute to the accumulation of fat in the liver and the pathogenesis of NAFLD, thus promoting the intestinal absorption of monosaccharides, and accelerating hepatic lipogenesis.

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Furthermore, the gut microbiota is involved in the regulation of NAFLD by microbial metabolites such as SCFAs [53]. However, research results are not consistent enough. Therefore, we need more clinical studies to address the composition, function, and the role of intestinal microbiota in the prevention and treatment of MDs.

There is more and more evidence which proves that an aberrant gut microbiota may be bidirectionally connected with HPA axis disturbances [54], chronic inflammation [39,55] and OxS exacerbation in tissues [56]. Therefore, it may serve as a link between MetS, depression and dysbiosis. Indeed, the GI microbiota can activate or attenuate the HPA axis through antigens, cytokines, prostaglandins or some metabolites that cross the blood-brain barrier (BBB) [54]. Dysbiosis alters the permeability of the gut barrier, and bacterial products can increase inflammatory cytokines and alter the BBB permeability inducing neuroinflammation [55,57,58]. Dysbiosis may also promote OxS both peripherally and in the brain by interfering with the local level of radical species and with the antioxidant system [56]. Additionally, it was found that supplementation with probiotics (live microorganisms which, when consumed in adequate amounts, confer a health benefit on the host [59]) decrease inflammatory markers in healthy and various disease conditions [60,61] and restore, directly or indirectly, oxidative balance [62,63]. A better characterization of the above associations represents a critical step at phenotyping, a preface to longitudinal clinical studies, and a more targeted approach to the treatment of DDs as well as MDs (Figure 1).

Figure 1

The patophysiological overlap between depresssive disorders (DDs) and metabolic disorders (MDs).

Green: common patophysiology of civilization diseases

* co-existance of DDs and MDs;

HPA: hypothalamic-pituitary-adrenal; CLGI: chronic low-grade inflammation; OxS: oxidative stress

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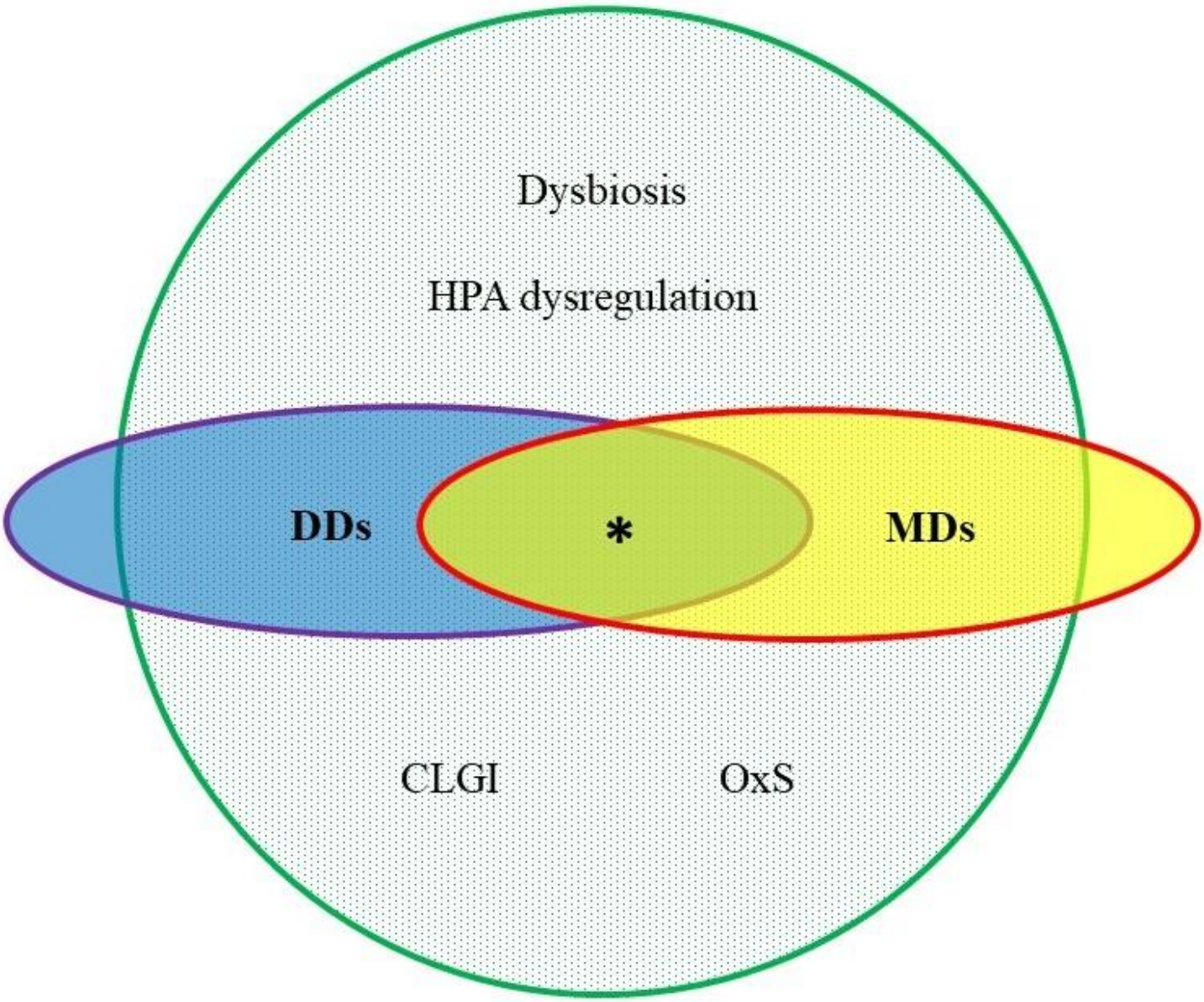

It should be underlined that different individuals can have taxonomically varied but functionally similar microbiota which makes functional co-assessment of microbiota health important [64]. One of potential microbial function biomarkers are SCFAs that are the most representative metabolites of fiber anaerobic fermentation. SCFAs are multi-target substances and can modify the activity of a variety of cells of the gastrointestinal, endocrine, metabolic, immune and nervous systems [65]. SCFAs are able to promote the function of the BBB and cerebral microglia, as well as increase the central expression of neurotrophic factors [66]. Interestingly, a depletion of SCFAs was reported in MDD patients [67], and their administration was shown to alleviate symptoms of depression in mice [68]. There is also some evidence that SCFAs can play an important role in regulating metabolic and cardiovascular health (reduced obesity, increased satiety factors level and improved insulin sensitivity) [53,69]. Altogether the above suggest that SCFAs may play an important role in metabolic-mood interaction although this has not yet been systematically explored.

So far, several possible interventions in our microbiotahave been made by introducing dietary and other lifestyle changes, supplementation with prebiotics (non-digestible carbohydrates that promote the growth of beneficial bacteria) or probiotics, fecal microbiota transplantation (FMT) [70,71]. Dietary fiber or fish oil intake is associated with prophylaxis and treatment efficacy in a range of diseases with CLGI as well as increased abundance of SCFA-producing bacteria. Proper diet, as an intervention targeting the microbiota, is an established way of alleviating symptoms of metabolic diseases [72], it is also perceived as an adjunctive method in the treatment of depression [73]. The

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same applies to other lifestyle factors - exercise and a regular routine appear to be associated with a harmonious bacterial ecosystem [74,75]. Results of research on prebiotics suggested a decreased fasting glucose, improved insulin sensitivity and lipid profile, reduced inflammation markers and modulation of neuroinflammation [76,77]. The main ways by which probiotics may work are through modulation of the immune system, antimicrobial substances, competition against pathogenic microorganisms, enhancing the intestinal barrier function, increasing the production of anti-inflammatory molecules and antioxidants and probably several others [78]. Recent meta-analyses of reports of trials using probiotics demonstrated their possible usefulness in depressive or anxiety outcome measures [47,79,80]. It has been suggested that the microorganisms can form a new group of drugs named "psychobiotics" [81]. However, there is too little consistency among study results, especially in terms of anxiety [82–84] and strain-dependence, and there is a need to conduct research with larger groups of clinical subjects. Furthermore, it has been summarized that probiotic intake may ameliorate some of the clinical components of MetS [85–88] as well as some inflammatory biomarkers associated with the syndrome [89,90]. Similarly, an improvement in clinical features as well as in OxS biomarkers was found in patients with type 2 diabetes mellitus (DM2) [62] or polycystic ovary syndrome (PCOS) [91] after probiotic supplementation. However, discrepant data regarding the health benefits of probiotics on metabolic diseases have been reported which may partially result from the heterogeneity of therapies and protocols. Finally, there appears to be evidence for the treatment of psychiatric disorders and MetS through FMT but the data is limited [92,93]. Further research with larger sample sizes and stronger scientific design is necessary in order to fully determine the efficacy and safety of this potential treatment. Apart from that, a growing number of medications have been found to affect the gut microbiota [94]. To sum up, standardised methodology (experimental design and data analysis) in microbiota intervention trials awaits further development and precise indications as to interventions that may modulate microbiota are yet to be discovered.

Current treatments for both depression and metabolic diseases remain suboptimal for many patients making improvements and advances in the intervention options in great demand. Whilst microbiota interventions may bring benefits to some individuals who do not fully respond to antidepressant medications, the target clinical sample for this intervention is not fully recognized. For psychiatrists it is essential to cooperate not only with psychologists but also with general practitioners, dietitians and other specialists. On research ground it would be worthy creating a scientific team working on complex relationships between mental health, metabolic disorders and the microbiota-gut-brain axis. An example team would include a psychiatrist with nutritional competence, a specialist of microbiology and molecular genetics, biostatistician specializing in microbiota evaluation, as well as a consulting dietitian, an internist and a psychologist.

Targeting GI microbiota composition and metabolic functions with natural and safe compounds, such as diet, exercise, pro- or prebiotics, to promote a healthier profile may undoubtedly be a useful tool for prevention and treatment of abdominal obesity and correlated diseases in patients with depression as well as for mood symptoms improvement.

Practical applications for future studies

There are several different definitions of depression applied in clinical and research practice [95]. According to the upcoming ICD-11 depressive disorders include single episode or recurrent depressive disorder, dysthymic and mixed depressive and anxiety disorder (MDAD) (Tab. 1). The new diagnosis, underlying its impact on patients everyday functioning and quality of life, is anxious depression [96]. Additionally, the ICD-11 includes the category of MDAD because of its importance in primary care settings and because of evidence of its overlap with mood symptomatology [97]. Therefore, it would be worth incorporating the whole category of DDs as a first step of eligibility screen in studies on new potential therapeutic methods for depressive patients.

Tab. 1

Depressive disorders in ICD-11

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6A70 Single episode depressive disorder
6A71 Recurrent depressive disorder
6A72 Dysthymic disorder
6A73 Mixed depressive and anxiety disorder
6A7Y Other specified depressive disorders
6A7Z Depressive disorders, unspecified

It is now agreed that in the case of MetS the criteria set by the International Diabetes Federation (IDF; Tab. 2) remains the most useful and widely accepted description of this cluster of metabolically related cardiovascular risk factors which also predict a high risk of developing diabetes (if not already present). The IDF definition and criteria address both clinical and research needs, providing a tool suitable for worldwide use [98]. In addition, the application of non-invasive markers of NAFLD, APRI and FIB-4 scores, to prognosticate liver dysfunction in this group of patients seems valuable in terms of stratifying patients and searching for biomarkers of a subpopulation sensitive to specific treatment. FIB-4 and APRI have demonstrated ability to risk stratify patients for liver-related morbidity and mortality, with comparable performance to a liver biopsy [99].

Tab. 2

The International Diabetes Federation (IDF) criteria of MetS

- Central obesity
  (defined as waist circumference* with ethnicity specific values; for Caucasian race: Male≥ 94 cm Female≥ 80 cm);

  * If BMI is >30kg/m², central obesity can be assumed, and waist circumference does not need to be measured

plus any two of the following four factors:

- Raised triglycerides ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
- Reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
- Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose ≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed type 2 diabetes

In terms of HPA axis abnormalities, CLGI, OxS and intestinal dysbiosis and according to the available data, it appears that there is no single marker to detect subtle alterations of these systems in depressive or metabolic diseases. On the contrary, the data indicate the need for multiple parameters. It might be useful to combine all endocrine,

inflammatory and microbiotic parameters to successfully predict this multidirectional complex leading to many years in disability or premature death.

In conclusion, it seems worth assessing the intestinal microbiota function and composition, HPA axis function indicators, CLGI markers or OxS parameters as potential bioindicators of depressive subpopulation sensitive to add-on treatment with microbiota interventions. Such a trial, if successful, could establish easy-to-use biomarkers for clinical practice. Given the personal and societal cost of treatment of civilization diseases, the research would contribute to advancement in health care over millions of people.

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Conflicts of Interest

The author declares no conflict of interest.

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