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Vitamin D, light and mental health

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ABSTRACT

Vitamin D receptors and vitamin D metabolizing enzymes are present in the central nervous system. Calcitriol (the active vitamin D hormone) affects numerous neurotransmitters and neurotrophic factors, relevant for mental disorders. In the case of depressive disorders, considerable evidence supports a role of suboptimal vitamin D levels. However, the data are not conclusive and further studies are necessary. Especially, the relative importance o\f the pineal–melatonin system versus the vitamin D-endocrine system for the pathogenesis of seasonal affective disorders is presently unresolved. Two diagnoses, schizophrenia and autism, have been hypothetically linked to developmental (prenatal) vitamin D deficiency, however, also in adult patients, low levels have been reported, supporting the notion that vitamin D deficiency may not only be a predisposing developmental factor but also relate to the adult patients' psychiatric state. Two cases are described, whose psychiatric improvement coincided with effective treatment of vitamin D deficiency.

1. Introduction

1.1. Historical background

Since the dawn of human history, the sun, springtime, warm weather and open, lightly shaded landscapes have been associated with happiness and positive feelings, in literature, visual art and religion. On the other hand, dark, urban environments, covered by heavily polluted skies are often associated with misery and fear, and also with the early industrialism's unimpeded exploitation. In such environments, rickets was first described, predating the discovery of vitamin D by almost three centuries. Without knowledge of the mechanisms, astute clinical observers identified remedies like countryside sojourns and cod liver oil. In the 1920s, vitamin D was identified, providing scientific foundation for treatments already in use, but also enabling more specific directions, like ultraviolet phototherapy (quartz lamps) and administration of purified vitamin D [1,2]. Among the symptoms of rickets, also mental symptoms were listed [3] and Florence Nightingale stated: "People say the effect [of sunlight] is on the mind. So it is, but the enlightened physician tells us it is on the body too." At that time, the mental effects of the sun seemed self evident; accordingly, the effect of rickets treatment on mental symptoms received little attention. Presumably these symptoms were mostly conceived as secondary to the somatic disability. Nevertheless, since rickets had been a widespread, observably crippling disorder, its disappearance as a public health problem became a stunning accomplishment of modern medicine, inspiring increased sun exposure in the first half of the 20th century.

From the 1950s an opposite trend has become notable, with increased indoor activities in all age groups, while sun exposure tended to be confined to holidays at sun-rich locations. Since the 1980s, the public has been cautioned against the sun's ultraviolet (UV) light, and parents are urged to protect their children from solar radiation in order to reduce the future risk of skin cancer (in particular malignant melanoma) [4]. In parallel with this change of UV exposure habits, an increasing prevalence of major depression in the US and in Europe has been reported, especially among children and adolescents [5,6]. More recently, an increased prevalence of autism spectrum disorders has been documented [7]. These epidemiologic trends may be relevant for the connection between vitamin D, light and mental health. This article is a selective review of research related to this.

1.2. Vitamin D in the central nervous system

The active form of vitamin D, calcitriol ($1,25(OH)_2$-vitamin D), is a seco-steroid (steroid molecule where one of the connected rings is cut open) with potent endocrine, paracrine and autocrine effects, induced by binding to its specific ligand, the vitamin D receptor (VDR). Like other hormones with nuclear receptors, it affects the gene expression of a multitude of target genes. The presence of VDR in the central nervous system (CNS) was discovered in 1982 [8]. There is now ample evidence that the necessary enzymes and receptors are distributed in different parts of the human brain

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[9], and that the vitamin D-endocrine system acts within the CNS as a neurosteroid with multiple actions [10–12]. Briefly, calcitriol interacts with the synthesis and degradation of some neurotransmitters, has an important role in the regulation of several neurotrophic factors and supports the brain's antioxidative defence.

Concerning neurotransmitters, calcitriol activates the gene expression of the enzyme tyrosine hydroxylase [13] (which is considered the rate-limiting step in the synthesis of the catecholamines), thereby increasing the availability of dopamine, noradrenaline and adrenaline. Also, calcitriol may enhance cholinergic function, both by increasing the activity of choline acetyltransferase [14] (the key enzyme for acetylcholine synthesis) and by decreasing the activity of acetylcholine esterase [15] (the enzyme that limits acetylcholine synapse transmission). Dopamine, noradrenaline and acetylcholine are well-known actors in the pathophysiology of e.g. mood disorders [16–18], attention deficit/hyperactivity disorders and Alzheimer's disease.

The next, and perhaps most prominent, role for vitamin D within the CNS concerns its influence on several neurotrophic factors. Thus, calcitriol is a potent enhancer of nerve growth factor (NGF) [19,20] and glial derived neurotrophic factor (GDNF) [21]. Also, it increases neurotrophin 3 (NT-3) and decreases neurotrophin 4 (NT-4) activity [22]. NGF is important for the developing brain prenatally, but is also believed to counteract degeneration of the cholinergic system in Alzheimer's disease [23]. In psychiatry, much research has focussed on brain derived neurotrophic factor (BDNF, not regulated by vitamin D), but recent research has shown that NGF, NT-3 and GDNF may also be involved in both depression and schizophrenia [24–28]. In addition, GDNF, strongly linked to dopaminergic functions, has a postulated therapeutic potential in Parkinson's disease as well as dependence disorders [29,30].

Finally, vitamin D participates in the brain's defence against oxidative degeneration. It increases the gene expression of γ-glutamyl transpeptidase, an enzyme contributing to the formation of glutathione, the most important antioxidant of the brain, and, consequently, increases glutathione levels [31]. In different animal models, calcitriol protects against neurotoxicity induced by methamphetamine, 6-hydroxydopamine or glutamate [32–35].

Based on this evidence, changes of vitamin D availability and the resulting changes in its endocrine system have a considerable potential to interfere with diverse brain functions, relevant to psychiatric and neuropsychiatric disorders. Since vitamin D levels are related to sun (UV-B) exposure, mental disorders with seasonal patterns should be investigated for possible vitamin D involvement (see Section 2). Considering the influence of vitamin D on neurotrophic factors, long-term vitamin D insufficiency may also be associated with aberrant early brain development (see Section 3.1) as well as late-life brain degenerations.

2. Seasonal variations of vitamin D supply and affective disorders

2.1. Seasonal affective disorder and light deficiency

Depressive disorder is a major cause of disability worldwide. The pathophysiology behind depression is far from disentangled. Most researchers in the field believe that many different factors contribute, and it has often been claimed that depressive disorder actually represents a heterogeneous mixture of disorders with different causations. In his treatise on mental disorders [36], the Paris 19th century physician Esquirol begins his chapter on treatment of major depression ("lypémanie ou mélancolie") with a case report. A man of 42 years had, in spite of happy life circumstances, for 3 years, suffered from recurrent symptoms of low spirits from autumn to spring. He would then neglect his work and family, feel weak, irritable and apathic, and resort to drinking alcohol, while in the summer he had none of those symptoms. Esquirol's successful prescription for him was to leave Paris in September for south France, then in October continue to Italy, and return to Paris in May. This case illustrates one of the purported depressive subtypes, seasonal affective disorder (SAD), and a treatment modality that might still be worth considering. SAD, whose modern definition appeared in 1984 [37], is characterised by depressive symptoms regularly recurring at the same time of the year. In research almost all studies have been confined to SAD, winter type, i.e. depression recurring in the darkest time of the year. Winter depressions often present with "atypical" symptoms, e.g. hypersomnia, hyperphagia, anergia and evening worsening. Light deficiency has been hypothesized as causative; hence, light treatment, phototherapy, seems logical. In spite of more than 25 years of research in this field, however, no consensus on the value of phototherapy in SAD has been attained. While some meta-analyses and reviewers claim that light treatment is highly effective in SAD [38,39] and recommend it as first hand treatment, others [40] conclude that "The value of therapy with a light box for seasonal affective disorder (SAD or seasonal depression) can be neither confirmed nor dismissed."

One major obstacle in phototherapy research is the inherent unfeasibility of providing a credible placebo condition, which could be used in double-blind comparisons with visible light entering the eye, the supposed necessary mode of action. Since it has repeatedly been shown that phototherapy patients' expectations are related to their outcome, prevalent placebo response cannot be excluded. Other problems are that several different methodologies compete, many of the studies have been undersized and that the pathophysiologic mechanisms are still not understood. According to the prevailing theories [41], SAD is related to dysregulation of some of the mechanisms responsible for circadian and seasonal rhythms: The shorter daily photoperiod of winter, or a phase-delay of diverse mechanisms connected to circadian rhythms, or suboptimal light input due to subsensitive retinal photoreceptors, or other mechanisms may perturb the function of the suprachiasmatic nucleus (SCN), the main regulator of circadian rhythms, a pacemaker interacting with the pineal gland and melatonin secretion. Then, the resulting disarray of these functions may interact with the individual's neurotransmitter availability and affective vulnerability to cause winter SAD. However, most of these hypotheses concerning the pathophysiology of SAD and phototherapy have been unsupported when judiciously tested. Measures of the circadian pacemaker or melatonin secretion have not been consistently different between SAD patients and controls, and associations between phototherapy induced changes of these measures and symptom reduction have been elusive [42,43].

In several studies (e.g. [44,45]), the placebo conditions, dim red light or invisible infrared light, were equally effective to bright light. Thus, the concept that visible light must enter through the eyes has been disputed. It is based on one single study [46] of 10 patients that were treated with covered skin or covered eyes in the evening, a treatment timing that is now generally believed to be less effective. More patients responded to eye than to skin treatment, but the patients' expectations and outcome overlapped to a great extent in this small, unblinded study. Based on this, patients have been instructed to direct the light towards their eyes during phototherapy, implying that skin exposure is superfluous. Concering the possible involvement of vitamin D in phototherapy, see Section 2.2. The suggestion, that extraocular light (e.g. through the skin behind the knee) may participate in circadian regulation, has been refuted [47,48], while another issue, whether specific retinal receptors not involved in conscious vision, utilizing cryptochrome as light sensor, conveys light information to the SCN [49], is still unsettled.

In view of all these inconsistencies and uncertainties, it is not surprising that phototherapy for SAD, as presently administered, is often insufficiently effective in long-term clinical praxis [50]. On the other hand, the successful development of a melatonin agonist, agomelatine, as an antidepressant [51], supports the idea that light conditions and the circadian regulation of the SCN are closely related to the pathophysiology of depressive disorders in general, and SAD in particular [52,53].

2.2. Vitamin D and depressive disorders

The well documented seasonal changes of 25-hydroxyvitamin D (25-OHD) and the numerous CNS actions of calcitriol make vitamin D an interesting candidate to explain seasonal mental health problems. Indeed, several studies of SAD and phototherapy have addressed the question of light wavelength and the possible role of vitamin D. The widely held conclusions from these studies have been that UV light does not contribute to efficacy [54] and that vitamin D is not involved [55]. Accordingly, in current phototherapy, UV light is filtered away, the patients may be fully dressed and only negligible amounts of vitamin D are formed [56]. On a closer scrutiny, however, these conclusions may have been drawn prematurely, especially in the light of recent findings from vitamin D research:

Concerning the UV wavelengths, three studies, summarized in Table 1, have addressed this: In the first [57], UV light was filtered at the light source; in the other two [58,59], the "non-UV" patients wore UV-filtering eyeglasses, while their skin was exposed. One study [59] had an UV-A source added to non-UV light, the others used broad spectrum light, including both UV-A and UV-B. The UV-A study was unable to show any differences between groups. Since they had studied whether additional UV-A (which does not contribute to vitamin D synthesis) into the eye was any better than UV-A only to the skin, the outcome was unsurprising. The authors [59] and a later meta-analysis [54] conclude: "the UV spectrum does not offer any clinical advantages to light therapy for SAD." From Table 1, though, it appears that treatment conditions with skin UV-B exposure, potentially boosting vitamin D, were superiorly effective in reducing the atypical symptoms of depression, often described as the most prominent symptoms of SAD. Thus, it seems possible that, at an early stage, UV-B radiation was excluded from SAD phototherapy, based on inadequate interpretation of study results. Concerning vitamin D biochemistry, one study was obviously performed in order to test whether vitamin D was involved in SAD or not [54]. The authors chose not to measure 25-OHD, which was already established as a measure of vitamin D status. Instead they measured calcitriol in the blood of SAD patients and controls before and after bright light therapy and found no significant differences. Since calcitriol is not a measure of vitamin D availability, and the brain has its own capacity to form calcitriol from 25-OHD [9], these findings are not informative.

The hypothesis that vitamin D may have a central role in depressed mood, SAD and phototherapy, was stated by Stumpf and Privette [60]. Subsequently, several studies have tested this concept: In a double-blind study [61], vitamin D3 caused a more positive mood in healthy individuals during winter. In a study of 15 SAD patients, 100,000 IU of vitamin D was more effective than 3 weeks of light therapy [62]. The amelioration of depression was significantly correlated with the increase of 25-OHD. This was also the case in an open study [63], where six patients were treated in winter with vitamin D 5000 IE/day. The three subjects that reached a final 25-OHD level above 100 nmol/l responded while the others did not. Two larger studies [64,65] failed to show efficacy of vitamin D, but they used considerably lower doses (400–800 IE/day) and it is unlikely that they reached the necessary blood levels. Two population based studies from Europe support a relation, irrespective of season, between lower 25-OHD levels and depressed mood [66,67], while one from China did not [68]. Four clinical samples [69–72] of patients with psychiatric diagnoses (including major depression) showed generally lower 25-OHD levels compared to controls or general population, with similar range (mean/median 40–50 nmol/l) for depressed patients across studies. Also, two more randomized trials, none of them focussing on diagnosed major depression, nevertheless support a mood elevating effect of vitamin D treatment [73,74].

Altogether, these findings support (but do not confirm) the hypothesis that low availability of 25-OHD may be causally related to a substantial proportion of depressive disorders [60–63,70,75–77]. One important confounding factor is the retinal-SCN-pineal (RSCNP) axis of light detection, which, similar to the vitamin D-endocrine system, co-varies with seasonal and latitudinal environment. A difference between these is that vitamin D functions usually are lagging 1–2 months after the light nadir [78,79], while RSCNP functions are direct. Serotonin is believed to be important in the pathophysiology of depression, there is ample evidence for a seasonal influence on serotonergic functions [80–84], and some of the serotonin findings seem more directly linked to the light nadir [83,84] and change with phototherapy [85]. Clinically, typical cases of SAD, winter type, seem to peak at the darkest time, but a considerable proportion of affective patients have a propensity for spring depressions, which coincides more closely with the vitamin D nadir. Accordingly, changes in serotonin may be more related to winter depression, the RSCNP axis and the effect of visible light, while spring depression may be more related to vitamin D insufficiency and non-serotonergic mechanisms. Alternatively, the 25-OHD drop required to cause mood symptoms may differ between individuals (see Fig. 1), in which case both winter, spring and some chronic depressions could be related to vitamin D availability. Psychopharmacological studies of SAD are not infor-

Table 1
Comparative trials investigating whether UV-light contributes to the effect of phototherapy in SAD: potential vitamin D production under trial conditions is estimated based on the described methodology of phototherapy (UV-B exposure of skin or not).

Study-arm		Light source		Subject exposure		**Vitamin D production**	Effect on Ham-D	**Effect on Atyp**
		UV-A	UV-B	Skin	Eye			
Docherty [56]	Active	+	+	+	+	**+**	=	**+**
	Control	–	–	–	–	–	=	–
Lam [57]	Active	+	+	+	+	**+**	+	**=**
	"Control"	+	+	+	–	**+**	-	**=**
Lam [58]	"Active"	+	–	+	+	–	=	=
	"Control"	+	–	+	–	–	=	=

Ham-D = Hamilton's depression rating scale, measuring general depressive symptoms.
Atyp = 8-item atypical depression scale, measuring hypersomnia, hyperphagia, anergia etc.
Effect results are presented as + and –, respectively, when there was any significant difference between study arms, otherwise as =.

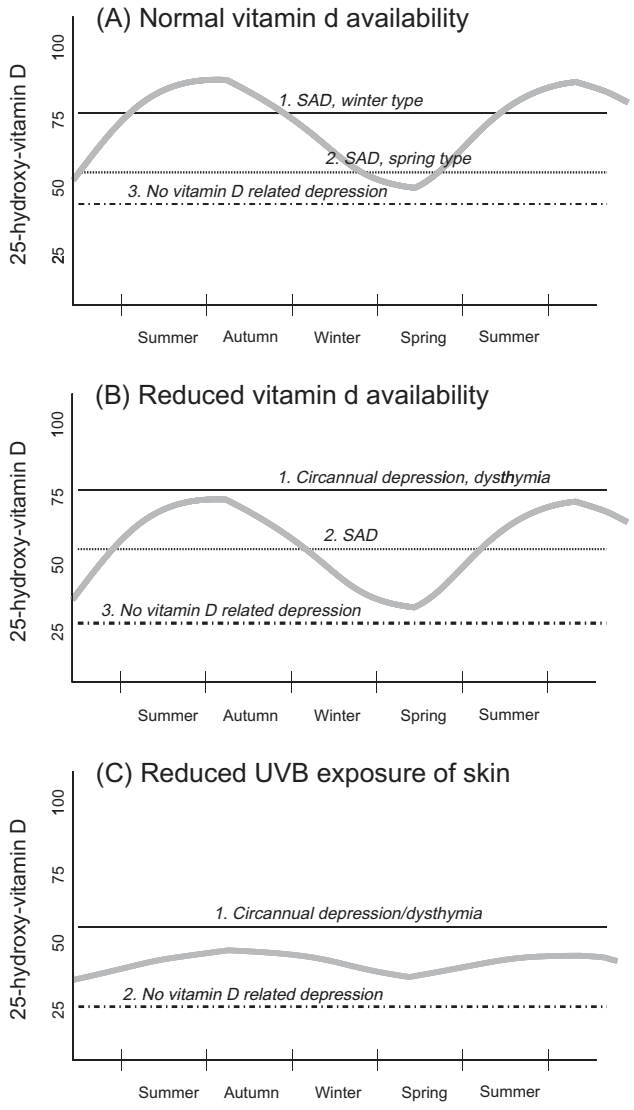

Fig. 1. Hypothetical relationships between depressive disorders and the seasonal pattern of 25-hydroxyvitamin D status in temperate regions (——), where the vitamin D nadir lags 1–2 months after the midwinter light nadir. A represents normal seasonal variation; in B, the individuals have a decreased vitamin D availability for e.g. dietary or metabolic/genetic reasons. In C, the seasonal pattern is levelled out because of reduced UV-B exposure, related to life style or skin pigmentation. Seasonal depression and some other depression types may hypothetically be linked to these patterns, assuming that individuals differ in terms of how their mood state is affected by vitamin D status; some individuals react to slight decreases (A1, B1), some get depressed from more substantial decreases (A2, B2, C1), while others do fine even at low levels (A3, B3, C2). Different black lines represent the susceptibility boundary for these groups of individuals, respectively.

mative, since both serotonergic and catecholaminergic mechanisms have been demonstrated [86,87]. Based on the preclinical findings of vitamin D in the CNS (see Section 1.2), a reasonable hypothesis is that serotonergic dysfunctions are more RSCNP related, while catecholaminergic dysfunctions are more likely to depend on vitamin D. One common symptom of depression, decreased libido, has been difficult to reconcile with the serotonergic deficit hypothesis, since increased serotonergic activity normally decreases sexual activity [88], which is consequently an expected side effect from serotonergic antidepressants. In contrast, this is not a side effect of vitamin D treatment, and recent research rather implies that vitamin D enhances reproductive functions [89,90], which makes the vitamin D deficit hypothesis more likely to explain this part of depressive symptomatology.

Concerning latitudes and SAD, an increased prevalence on higher latitudes has been claimed [91]. In a later meta-analysis [92], this was supported within North America but not in Europe. A series of meticulous studies have unsuccessfully tried to explain why the SAD prevalence on Iceland and among Icelandic migrants in Canada is lower than expected from the latitude [93,94]. However, the possibility that vitamin D is involved was not explored. Since Icelanders have high fish consumption and a large proportion of them traditionally use fish oil supplementation, it is hardly farfetched to assume that those prone to SAD may have used this to boost their vitamin D status, and that vitamin D involvement in SAD explains this Icelandic paradox.

In conclusion, a large amount of studies have tried to elucidate the mechanisms behind SAD and phototherapy, but there is a dearth of studies concerning vitamin D in these patients. The presumed associations between season/latitude and SAD may to a great extent have been blurred by modern life style, involving e.g. more artificial light in everyday life and holidays at sunny latitudes, but also increased indoor activities and sun avoidance. Because of this, the distinction between SAD and other depressive disorders have become even more difficult to disentangle. In any case, it seems clear that serotonin, catecholamines, RSCNP axis and vitamin D may all be involved to various degrees. In view of the substantial number of depressed patients that do not respond to evidence based therapy [95], a check for vitamin D deficiency and treatment if relevant, aiming at 25-OHD levels above 100 nmol/l, seems justifiable. Otherwise, many of them revert to self-treatment: In a study of "hardcore, frequent indoor UV tanners" [96], it appeared that 80% of them had symptoms of SAD, and their tanning was described as an addictive behaviour. It was even demonstrated [97] that frequent tanners, under blind conditions, could distinguish UV from non-UV light and preferred the UV tanning bed. This could hypothetically be related to conditioning of the brain's reward system, induced by the dopaminergic actions of calcitriol.

2.3. Case report: seasonal affective disorder

A 52 year old man had experienced yearly recurrences of depression for many years. Usually, the onset was gradual in late October. From December to March, almost every year, the depression was moderately severe, with low mood, asthenia, lack of interest in most activities, decreased libido, and hypersomnia. Most of the time, he had continued to work in spite of these symptoms, however, at the cost of almost all other activities. Between April and September he was usually in a good mood, with lots of activities, however, no symptoms of mania were reported. During the years, he had been treated with three different antidepressants and two different psychotherapies with only minor results. Light treatment, however, had not been available.

This year, he was treated with cholecalciferol 4000 IU/day, and for the first time experienced at distinctly positive treatment result. This was also testified by his wife. Only after the treatment, did we receive his pre-treatment 25-OHD result, 74 nmol/l, very close to the recommended level. After 2 months treatment his level was 97.

It was concluded that this man was sensitive to relatively minor decreases of 25-OHD levels. See Fig. 1A1.

3. Prenatal vitamin D supply and neurodevelopmental psychiatric disorders

3.1. Brain consequences of developmental vitamin D deficiency

A common feature of schizophrenia and autism is that research has demonstrated quite substantial changes not only in brain func-

tion, but also in brain structure and morphology [98,99], presumably related to disturbance of the prenatal development. There is growing evidence that calcitriol is involved in brain growth and development during fetal life [100–102]. Studies on rats have shown that vitamin D deficiency not only interferes with brain development during the fetal period but also leads to permanent changes in the adult brain [103]. In a review of animal and human studies it was recently concluded that vitamin D is "essential for normal brain function" during fetal development and early infancy [104].

3.2. Epidemiological and other support for a link between developmental vitamin D deficiency and adult schizophrenia

Poor nutrition during pregnancy increases the risk that the child will later develop schizophrenia [105,106]. There is still no consensus on which nutrient is most important for this effect, but vitamin D can definitely be counted as one of the leading candidates. In the case of schizophrenia, ample evidence from epidemiology and preclinical research supports the hypothesis of a link between vitamin D deficiency during fetal development/early childhood and severe mental illness, schizophrenia, later in life [107–109]. Thus, studies have shown that individuals born during winter and spring (i.e. when vitamin D levels are at their lowest) have a higher risk of developing schizophrenia [110]. Furthermore, children born at higher latitudes have a higher risk of developing schizophrenia [111,109], especially if they have darker skin pigmentation and consume less fish [109], factors that predict poorer vitamin D status. Also, vitamin D supplementation during the first years of life is associated with a reduced risk of schizophrenia among men [112]. Finally, schizophrenia is more common among those that grew up in urban areas [113], where sun exposure may have been reduced relative to the countryside.

3.3. Clinical findings in adult schizophrenia with relevance for vitamin D

Two small studies of inpatients or outpatients with schizophrenia showed decreased levels of 25-OHD [69,72]. In an epidemiological case-control study, however, individuals with psychosis did not differ from controls [114]. Migration is an established risk factor for schizophrenia, at least in Europe and Canada [115,116]. However, the risk is most elevated in dark-skinned immigrants, i.e. those at highest risk of vitamin D deficiency [117,118].

Persons with schizophrenia have an increased morbidity and mortality compared to the general population [119]. The causation of this is a matter of debate. At least some of the antipsychotic medications, foremost olanzapine and clozapine, may cause metabolic adverse effects that are very similar to the metabolic syndrome [120]. It has also been argued, however, that an increased risk for diabetes type 2 is inherently related to schizophrenia per se. In research of the pathophysiology behind these adverse effects, several different hypotheses have been tested, e.g. various gene polymorphisms that may relate to the pharmacodynamics or pharmacokinetics of these drugs. In view of the associations between the metabolic syndrome and hypovitaminosis D [121,122], it is here hypothesized that low availability of calcitriol may somehow be related to these adverse effects. In support of this, several US studies report that these adverse effects have been more common among Afro-Americans (e.g. [123]), well known from other sources to have significantly lower levels of circulating 25-OHD.

Most research on vitamin D in schizophrenia has focussed on the predisposing importance of prenatal vitamin D deficiency. It cannot be excluded, however, that the present state of these patients in clinical psychiatry is influenced by their vitamin D status [72,118] (see also Section 3.5).

3.4. Epidemiological support for a link between developmental vitamin D deficiency and autism spectrum disorders

It has subsequently been suggested that a series of findings support a similar hypothesis of early vitamin D deficiency and the development of autism [124]. For instance, the prevalence of autism in the United States has increased over the years that the public has been recommended to avoid sun exposure. Furthermore, in rainy areas with less hours of sunshine, more children with autism are born. Such a relationship between annual precipitation and the frequency of children with autism has been found in Washington State, Oregon and California [125]. Some genetic features of autism disorders are also compatible with an additional vitamin D hypothesis: that vitamin D prevents the occurrence of spontaneous mutations in germ cells [126]. According to these researchers, a predisposition for autism could result from genetic damage in spermatozoa, and there are some data supporting that vitamin D may prevent such damage. As in the case of schizophrenia, immigrant groups in northern Europe with high prevalence of vitamin D deficiency also have a higher rate of autism [127–129]. Much more research, however, is necessary, in order to draw conclusions about the vitamin D – autism connection.

3.5. Case report: immigrant with schizophrenia

A 26-year old female, of Middle East origin, had immigrated to Sweden 2 years before I saw her. According to relatives, she had suffered one or two very brief, self-limited psychotic episodes in her home country. About ½ year after arriving in Sweden, she developed a severe psychosis with voice hallucinations and was admitted to a psychiatric hospital. She was diagnosed as schizophrenia but despite intense antipsychotic treatment for about 6 months, she remained psychotic and hallucinating, and sent home to her relatives in this state. When I saw her, she was severely psychotic (Clinical Global Impression-Severity (CGI-S) = 7), unable to communicate, and with constant hallucinations, in spite of 20 mg/day of olanzapine. Her relatives were very concerned about her state and made sure that she complied with the medication. She also suffered from musculoskeletal pain and had a gait. Her 25-OHD was 13 nmol/l and her intact parathyroid hormone (iPTH) was elevated.

After 4 months treatment with 1600 IU D3 + 1000 mg Ca, her psychiatric state was dramatically improved (CGI-S = 3); she could express herself through the interpreter, had plans for a future in Sweden and her gait had disappeared. Her 25-OHD had increased to 73 nmol/l and iPTH was normalized. After 6 months she was able to start studying Swedish for immigrants. She was still treated with antipsychotic medication, but the dosage had been gradually reduced.

The psychotic state of this first-generation immigrant had led a mild course while she was living in a sunny country, but in Sweden she developed a severe, treatment-resistant state. Despite unfavourable psychosocial circumstances (her relatives tried to help her appeal against a deportation order), her mental state improved dramatically during treatment with vitamin D and calcium. It is, of course, possible that the treatment coincided with an amelioration that was part of the disorder's natural course. It might also be the case that her elevated iPTH played a role, and that the additional calcium helped to normalize this, in spite of the rather low dose of vitamin D. The case suggested, however, that vitamin D deficiency may have contributed considerably to the severity of her psychotic state.

4. Conclusion

In conclusion, vitamin D deficiency may affect mental health through several different mechanisms: A deficiency may cause

temporary discomfort, depression and fatigue (which are normalized when the deficiency is restored) in otherwise healthy individuals, a mechanism that may be relevant in seasonal affective disorders (winter and spring depressions). Secondly, a deficiency during fetal life and childhood may affect brain development, resulting in a more permanent impairment of brain functions, a mechanism that may be relevant for schizophrenia as well as autistic disorders. In addition, vitamin D deficiency may, hypothetically, have a negative influence on parental germ cells prior to conception, a mechanism that has been suggested for autistic disorders. (Vitamin D may also, through neuroprotective effects, counteract neurodegenerative disorders, e.g. Parkinson's and Alzheimer's diseases, which are beyond the scope of this review.) However, for each of these mechanisms, much research remains to be done in order to conclude on their validity. Meanwhile, it seems reasonable that detecting and treating vitamin D deficiency among psychiatric patients will counteract some of their elevated somatic risk factors, e.g. the increased risk of osteoporosis imposed by common antidepressant and antipsychotic drugs [72,130–133].

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