

What is the role of vitamin D in autism?

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A growing body of literature suggests that higher serum 25-hydroxyvitamin D [25(OH)D] concentrations, either in utero or in early life, may reduce the risk of autism. For example, an ecological study in the companion paper inversely correlated solar UV-B doses in the United States with prevalence of autism among those aged 6–17 y. That study proposed that vitamin D deficiency during pregnancy could account for this finding, although the findings are also consistent with childhood vitamin D deficiency contributing to the condition. Also, in a recent study, children with autism had lower serum 25(OH)D concentrations than did control subjects (19 vs. 33 ng/ml), despite parents of each group reporting the same amount of sun exposure. The same study found highly significant inverse correlations between 25(OH)D and autism rating scales and between 25(OH)D and levels of an antineuronal antibody. This finding indicates that higher serum 25(OH)D concentrations may reduce the symptoms of established autism. Because activated vitamin D, a secosteroid, upregulates DNA-repair genes, vitamin D deficiency during development may inhibit the repair of de novo DNA mutations in fetuses and infants and thus contribute to risk of autism. Vitamin D might also reduce the risk or severity of autism through its anti-inflammatory actions, antiautoimmune effects, increasing seizure threshold, increasing T-regulatory cells, protecting the mitochondria, and upregulating glutathione, which scavenges oxidative by-products and chelates (captures and excretes) heavy metals. Vitamin D deficiency during pregnancy and childhood is a widespread and growing epidemic.

Perhaps because of the term *vitamin*, most people wrongly assume that vitamin D is like other vitamins—that is, they can obtain adequate amounts by eating a good diet. However, the natural diets most humans consume contain little vitamin D, unless those diets are rich in wild-caught, fatty fish.¹ Fortified foods, such as milk, orange juice, and cereals in the US, and margarines in Europe, contain small amounts of vitamin D, but such sources are usually minor contributors to vitamin D stores. Traditionally, the human vitamin D system began in the skin, not in the mouth.

The manufacture of vitamin D by skin is extraordinarily rapid and remarkably robust; production after only a few minutes of midday, midlatitude summer sunlight easily exceeds dietary sources by an order of magnitude. Incidental sun exposure, not dietary intake, is the principal source of circulating vitamin D stores and to a degree that is a function of skin surface area exposed. For example, when fair-skinned people sunbathe in the summer (one full-body, minimal erythral dose of UV-B [UVB] radiation), they produce more than 20,000 IU of vitamin D in less than 30 min.² One would have to drink 200 glasses of American milk (100 IU/8-oz glass) to obtain this amount orally.

Vitamin D normally enters the circulation after UVB from sunlight strikes 7-dehydrocholesterol in the skin, converting it through thermal energy to vitamin D₃, or cholecalciferol (vitamin D). When vitamin D is taken by mouth, the body

metabolizes it similarly to that generated in the skin. No matter how it arrives in the circulation, the liver readily hydroxylates vitamin D to 25(OH)D, the circulating form of vitamin D.

The classic endocrine function of vitamin D begins when the kidney further hydroxylates 25(OH)D into 1,25(OH)₂D (calcitriol), which then acts to maintain serum calcium level through a series of direct effects on calcium absorption and excretion, and through a series of interrelationships with serum phosphate and parathyroid hormone. Serum calcitriol levels are generally in the reference range, or even high, when 25(OH)D levels are low, except in extreme vitamin D deficiency.² Furthermore, endocrine calcitriol is an adaptive hormone (i.e., it is produced in response to calcium deficiency); calcitriol levels are typically low when calcium intake is high.

In the past 15 y, research has found that the vitamin D steroid hormone system includes more than this classic endocrine pathway used to preserve the calcium economy. The cytochrome P450 enzyme, which further hydroxylates 25(OH)D to calcitriol, is present in a wide variety of human tissues other than the kidney. That is, the hormone directly affects many cells and tissues via its autocrine, and presumed paracrine, functions. Like all steroid hormones, calcitriol acts as a molecular switch, activating many target genes via the vitamin D receptor (VDR). Most organs in the body show evidence of end-organ responsiveness to calcitriol, including multiple areas of the brain.³

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Vitamin D and the Genetic Foundation of Autism

Geneticists have fruitlessly looked for a common genetic mutation that causes most autism. The common *de novo* point mutations they do find are associated with only a small percentage of cases. In 2008, Cannell proposed a new theory for the genetic component of autism that involved the quantitative genetics of the vitamin D system.⁴ Any viable and parsimonious theory must explain the genetic components of autism, which toxicologists often ignore.

To explain the new vitamin D–related genetic theory of autism, we will analyze a recent study of a putative vitamin D–related disease, atherosclerosis, and one of the inherited components of the vitamin D system, the VDR. In apparently unique research, Schnatz and colleagues wanted to know whether the heritable variation in the expression of VDRs in coronary arteries was associated with the severity of atherosclerosis.⁵ They gave 39 cynomolgus monkeys 1,000 IU of vitamin D₃/day and an atherogenic diet for 3 y. The researchers then quantified the expression of VDRs inside the monkeys' arteries and measured the height of the atherosclerotic plaque therein. They found a strong negative association ($p < 0.001$): the fewer VDRs inherited, the worse the atherosclerosis.

Another paper found significant changes in composite health outcomes (cancer, death, hip fracture, or myocardial infarction) with respect to a combination of serum 25(OH)D concentrations and VDR alleles. Having low serum 25(OH)D concentration and two minor alleles was associated with a hazard ratio as high as 1.82 (95% confidence interval, 1.31–2.54); for having no minor alleles, the ratio was 0.93 (95% confidence interval, 0.70–1.24).⁶

The Schnatz study describes exactly the genetic mechanism proposed for the autism epidemic. Quantitative genetic (not qualitative mutations) variations in some facet of vitamin D metabolism, such as VDR or in the enzyme that activates vitamin D, may explain the heritability of autism. A study of 510 middle-aged, male twins (310 monozygotic and 200 dizygotic twins) found that, in the winter only, more than 70% of human 25(OH)D serum levels are heritable.⁷ The same authors found no contribution of genetic factors to individual differences in serum 25(OH)D concentrations during the summer, finding summer 25(OH)D similarities between twins were mostly attributable to a shared environment.

However, these twins were unusual; they had mean wintertime 25(OH)D levels of 30 ng/ml and mean summer levels of 50 ng/ml, levels few autistic children ever obtain. Studies show much lower 25(OH)D levels in autism.⁸ Furthermore, another recent study not only found much lower levels in autistic children (mean of 15 ng/ml compared with 30 ng/ml in controls), it also found an extremely strong correlation coefficient ($R = -0.84$) between vitamin D levels and severity on autism rating scales ($p < 0.001$).⁹ These same authors found that, despite the same amount of sun exposure, Saudi Arabian autistic children had vitamin D levels about one-half that of normals controls. When combined with the heritability twin study mentioned above, this appears to imply that vitamin D levels in autistic children are highly heritable.

People inherit either a little or a lot—with most somewhere between, as described by Gaussian distribution—of the genetic products of the vitamin D system.¹⁰ That is, the components of the vitamin D system [the enzymes that make 25(OH)D and

calcitriol, the number of VDRs, the vitamin D–binding protein that transports vitamin D around the body, and the enzyme that breaks down vitamin D] are all under genetic control. People inherit their relative quantitative functionality or dysfunctionality, and that becomes extremely important to the brain if vitamin D levels are low, as they are in autistic children.¹¹

For example, say that someone inherits a small number of VDRs in the brain. Unfortunately, the mother believes in strict sun avoidance and sunblock. She breast-feeds the child (breast milk lacks vitamin D) and then weans him on fruit juice (also without vitamin D). Moreover, he will not eat cold-water fatty fish, reindeer meat, or seagull eggs (foods high in vitamin D). This child literally has no source of vitamin D substrate to make calcitriol. Also, he was unlucky enough to inherit a small number of VDRs, which will interact with the low vitamin D level to injure the developing brain, just as it injures the arteries of monkeys. The same mechanism can operate *in utero*. Thus, the child has an epidemic of a “genetic” disease, as autism is, interacting with the environment, as autism does, to create a rapidly rising genetic disease. Although the genetics of the vitamin D system have been present throughout history, the small amount of substrate (vitamin D) is brand new (the vitamin D–deficiency epidemic) and is thus a new apparent “genetic” epidemic.

Xu and colleagues recently wrote that you may well have a genetic disease that you did not inherit.¹² That is, you may well have *de novo* genetic mutations, such as those seen in autism and schizophrenia, which occurred while you were living (either *in utero* or as a young child) and that you did not inherit.¹³ That supposition explains the genetic findings of autism nicely, in that the most common genetic finding is multiple small genetic *de novo* mutations. It also explains the male-to-female ratio in the incidence of autism, which is about 5:1; because males experience more germ-cell divisions with age.¹⁴ (See also the review by Veltman and Brunner.¹⁵)

Genetic models of these data indicate that most of the observed *de novo* point mutations are not connected to the etiology of autism.¹⁶ A few are associated with increased risk, but they are distributed across many chromosomes and are not common or severe enough to explain the disease. In other words, the genetic defects in autism are often quite minor compared with what we have grown accustomed to think about, such as the extra entire chromosome that occurs in trisomy 21.

In the related paper, we reported an ecological study of autism prevalence among US adolescents with respect to solar UVB doses.¹⁷ Solar UVB was inversely correlated with prevalence, which was interpreted as most likely being due to vitamin D deficiency during pregnancy—probably in the third trimester, when the brain develops most rapidly. The discussion of DNA damage in this section further supports the finding of the ecological study.

Are the DNA Changes in Autism Effects Rather Than Causes?

Several proteins exist to constantly repair DNA. Researchers have identified at least five vitamin D–dependent genes that code for

DNA-repair proteins, whose only job is to fix mutated DNA.¹⁸ Fleet and colleagues reviewed DNA repair as one of vitamin D's mechanisms of action in cancer. Vitamin D has as many mechanisms of action as genes it regulates. According to Haliska and colleagues, DNA repair is one of vitamin D's repair and maintenance functions.¹⁹

Several mechanisms can damage human DNA.²⁰ The DNA molecule is inherently unstable. Oxidation, pollutants, toxins, and background radiation can also damage DNA. According to Ting and colleagues, calcitriol protects cells by upregulating DNA-repair genes that even help repair double-strand breaks.²¹ The authors elaborated that their research suggested that vitamin D guards the genome via control of DNA repair.

For example, take 8-OHdG, a marker of oxidative DNA damage. In a randomized controlled human trial, even the relatively small dose of 800 IU/day of vitamin D reduced 8-OHdG by 25%.²² Likewise, PARP is an enzyme in the nucleus that responds within seconds at damaged DNA sites and facilitates DNA repair. The problem is that too often PARP overreacts and starts damaging neighboring DNA unless vitamin D regulates it.²³ Finally, in a randomized controlled human trial, 800 IU of vitamin D significantly increased levels of Bax, which helps stop mutations by promoting apoptosis.²⁴

Thus, the widespread point mutations and de novo DNA damage seen in autism could be an effect, not a cause. It is the effect of a genetically impaired vitamin D system combined with inadequate amounts of the vitamin D building blocks. This causes widespread de novo point mutations, which for years have confused geneticists, who may have assumed that any genetic abnormality in autism was a cause and not an effect.

DNA Stability

As early as 2001, Chatterjee reviewed vitamin D and genetic stability.²⁵ Vitamin D at physiological concentrations protects cell proteins and cell membranes against oxidative stress by inhibiting the oxidative attack on membrane walls. She also reported that calcitriol stabilizes chromosomal structure and prevents DNA double-strand breaks. She concluded that calcitriol acts as a master stabilizer of the genome by its critical role in many processes involving DNA defense and repair.

Could vitamin D prevent DNA damage, protecting the genome? Nair-Shalliker and colleagues²⁰ recently reviewed in vitro, animal, and human studies, concluding that vitamin D protects DNA from mutations. Vitamin D stabilizes the genome by protecting the genome from the insults of daily life (inherent genomic instability, oxidative stress, and toxic damage). The researchers went so far as to say that vitamin D deficiency is associated with DNA damage due to various cellular stresses and that obtaining adequate vitamin D is important in preventing DNA damage. However, what is "adequate vitamin D," the unnatural levels (20 ng/ml) found in poleward-living indoor workers or the natural levels found in equatorial outdoor hunter-gatherers (50 ng/ml)?²⁶

Anti-Inflammatory Actions

Autism is also a disease of inflammation.²⁷ According to Guillot and colleagues, vitamin D confers profound anti-inflammatory actions.²⁸ Studies of animals show direct and indirect anti-inflammatory effects involving both the innate and the adaptive immune system. Guillot and colleagues report that vitamin D's overall effect is to serve as an immunomodulator that reduces inflammation while enhancing protective immune responses. Calcitriol modulates various immune cells, including monocytes, macrophages, dendritic cells, and T and B lymphocytes.²⁹

Proinflammatory chemokines, such as MCP-1, are consistently elevated in studies of autistic children, whereas another type of proinflammatory molecule, tumor necrosis factor α , is also increased in autistic populations.³⁰ However, Gao and colleagues showed that activated vitamin D consistently and markedly reduced the release of MCP-1.³¹ Meanwhile, Shedeed found that supplementation of infants with vitamin D markedly reduced TNF- α .³²

Calcitriol exhibits multiple anti-inflammatory effects.³³ It inhibits the synthesis and biological actions of proinflammatory prostaglandins, which are elevated in autism.³⁴ Calcitriol also exerts anti-inflammatory activity by inhibiting NF- κ B, which is involved in aberrant signaling in autistic brains.³⁵

An Autoimmune Disease?

More than 160 human autoimmune diseases exist, and autism appears to be among them, with several autoantibodies to brain identified in both fetuses³⁶ and autistic children.³⁷⁻³⁹ Furthermore, levels of such antibodies are directly associated with the severity of autism.^{40,41}

Munoz and colleagues⁴² recently concluded that most autoimmune disorders studied so far are somehow involved with vitamin D deficiency. According to Hayes and colleagues, a diverse and rapidly growing body of epidemiological, climatological, genetic, nutritional, and biological evidence indicates that the vitamin D steroid system helps to establish and maintain immunological self-tolerance.⁴³

In animal models of these diseases, vitamin D supplementation produces therapeutic effects.⁴⁴ Adorini and colleagues report that the net effect of vitamin D is to make the immune system less likely to attack the body's own tissues.⁴⁵ Thus, vitamin D may reduce autoantibodies in autism, although that supposition remains to be tested. A recent study inversely correlated the level of one antineuronal antibody (anti-myelin-associated glycoprotein) with 25(OH)D levels ($p < 0.001$).⁴⁶

The antiautoimmune effects of vitamin D may explain the reported epidemiological associations between vitamin D status and many autoimmune disorders.⁴⁷ Thus, vitamin D is a potential prospect for treating diseases with autoimmune involvement, such as autism.

Decreasing Seizures

Up to 25% of children with autism have seizures.⁴⁸ Calcitriol increases the seizure threshold in rats.⁴⁹ Correcting vitamin D

deficiency would help control seizures. In a recent open study,⁵⁰ eight of 13 seizure patients were extremely vitamin D deficient. The investigators then corrected vitamin D deficiency in all 13 subjects by administering a one-time dose of 40,000–200,000 IU of vitamin D3, followed by a 2,000–2,600-IU daily dose of vitamin D3 for 3 mo, depending on weight. This intervention reduced seizures by 40%. One subject started with a vitamin D level less than 4 ng/ml, and treatment raised his level to 43.1 ng/ml; over 3 mo, his total number of seizures dropped from 450 to 30.

The study's limitations include a small number of patients and the lack of a placebo. However, this study certainly warrants a follow-up randomized controlled trial, and it highlights the importance of correcting vitamin D deficiency in seizure patients, including autistic patients with seizures.

T-Regulatory Cells

T-regulatory (T_{reg}) cells suppress the reactions of other immune cells to prevent the body from attacking its own tissues. These regulatory T cells, sometimes known as suppressor T cells, are a subpopulation of T cells that calm the immune system, maintain tolerance to self, and are associated with less autoimmune disease.⁵¹ This immunomodulatory effect of vitamin D via T cells might underlie the associations of vitamin D deficiency and autoimmune diseases.⁵² Some authors now think that vitamin D may effectively treat certain autoimmune disorders by affecting T_{regs} , making the body more tolerant of self.⁵³ A recent study reported a deficiency of T_{regs} in 73.3% of autistic children.⁵⁴

Priehl and colleagues studied vitamin D's effect on the percentage of T_{regs} .⁵⁵ They gave 140,000 IU of vitamin D to 46 healthy subjects as a single dose and then repeated it at 4 weeks. They measured the percentage of T_{regs} at baseline and at 4 and 8 weeks. Vitamin D increased Treg percentage from 4.8 at baseline to 5.9 at 4 weeks and to 5.6 at 8 weeks. Both changes were highly significant. Of course, such treatment would depend on how much tissue remains in the organ under attack. With type 1 diabetes, virtually all the cells that make insulin are destroyed, so vitamin D offers little hope for a cure. However, to our knowledge, no studies indicate that the brains of autistic children are permanently damaged, although parts may be. Thus, vitamin D may make the body more tolerant by increasing T_{regs} .

Neurotrophins

Neurotrophins are proteins that induce the development, function, and survival of nerve and brain cells. Calcitriol upregulates neurotrophins, such as NGF and GDNF, up to 5-fold.⁵⁶ Vitamin D deficiency in utero caused lower levels of NGF.⁵⁷ Thus, vitamin D appears to be intimately involved in regulating neurotrophins. Could it increase neurotrophins in older autistic children and thus help a damaged brain develop properly?

Mitochondrial Protection

In autism, about one in 20 people with autism have frank mitochondrial disease and more are in the "gray zone," perhaps as

many as one in three.⁵⁸ However, the numbers could be higher because mild mitochondrial dysfunction is hard to document.

Recently, Garcia and colleagues tested a calcitriol analog, paricalcitol, to see whether it could protect the mitochondria when scientists injured the mitochondria in lab animals by stopping the blood supply to a kidney.⁵⁹ Biochemical, histological, and molecular readings suggest that the scientists successfully injured the mitochondria in both animals given placebo and those given vitamin D. However, mitochondria were larger and contained dilated crests and larger-than-normal spaces in their interiors in the group not treated with vitamin D, indicating worse damage; these changes were not present in the group not treated with vitamin D. Also, markers of mitochondrial damage reverted to normal in paricalcitol-treated animals within several hours. These results suggest that calcitriol may confer a protective effect at the mitochondrial level.

Antioxidants

Garcion and colleagues, and others, report that vitamin D upregulates the amount of glutathione in the brain.^{60–62} Garcion and colleagues conclude that vitamin D is intimately involved in the glutathione cycle via calcitriol's upregulation of γ -glutamyl transpeptidase, which is involved in glutathione metabolism. Once glutathione is used, it is split in two and needs to be reconstituted, which is the rate-limiting step in the production of glutathione, performed by γ -glutamyl transpeptidase.

Because glutathione participates in the scavenging of oxidative by-products and the chelation (capture and excretion) of heavy metals, they concluded that activated vitamin D was involved in detoxifying the brain.⁶³ Activated vitamin D reduces iron-induced⁶⁴ and zinc-induced⁶⁵ oxidative injuries in rat brain through depletion of glutathione and subsequent generation of reactive oxygen and nitrogen inflammatory species.⁶⁶ Besides its function as a master antioxidant, glutathione removes heavy metals, including mercury.⁶³ Glutathione protects nerve cells and nerve conduction critical to mental processing, especially from toxins.

Halicka and colleagues reported that recent gene profiling has revealed several more antioxidants whose genes vitamin D directly upregulates.⁶⁷ This includes thioredoxin reductase and superoxide dismutase, both of which, among other things, function as antioxidants and detoxification agents. Thioredoxin reductases are essential proteins for regulating antioxidant balance and limiting the damage due to mitochondrial oxidation. Superoxide dismutase, which splits superoxide into less damaging molecules, serves a key antioxidant role.

Comorbid Conditions

Diabetes is more common in autistic children and a double blind randomized controlled trial that showed 2,000 IU/day of vitamin D3 in adults decreased insulin resistance.⁶⁸ In a study of 85 non-autistic children, insulin resistance was 7-fold higher in children with 25(OH)D levels below 10 ng/ml, compared with children with levels above 30 ng/ml.⁶⁹ In the same study, mean

insulin levels were dramatically lower in the children with the highest vitamin D level, compared with the children with lowest levels.

Adiponectin is a peptide hormone secreted by fat tissue. Adiponectin levels are significantly lower in autistic children than non-autistic controls.⁷⁰ Adiponectin is also inversely associated with obesity. Adiponectin levels are positively associated with vitamin D levels.⁷¹

Conclusion

The search for the genetic basis of autism has been elusive. However, to our knowledge, no one has looked at simple variation in the quantitative genetic variations in various components of the vitamin D system. Those with low activity of various vitamin D enzymes and who suffer maternal or early childhood vitamin D deficiency would have low activity in the vitamin D system, which is crucial to brain development.³

In addition, various tenable mechanisms exist for how vitamin D could help children with autism. Be it via DNA repair, anti-inflammatory actions, antiautoimmune activities, antiseizure

activity, increase in regulatory T cells, mitochondrial protection, or stimulation of antioxidant pathways, adequate doses of vitamin D (enough to obtain natural levels) are a potential preventive agent for autism, and even higher doses may be a potential treatment for established autism.

An open label clinical trial testing large vitamin D doses in autistic children as a new treatment modality is current recruiting at UCSF with target 25(OH)D levels of 80 ng/ml.⁷² As the recent Kocovská review pointed out, vitamin D deficiency is the norm in autistic children.⁸ Given that fact, treatment of vitamin D deficiency in autistic children should proceed now, with target mean 25(OH) D levels in the median to high natural range (50–80 ng/ml).²⁶ In addition, randomized controlled trials are urgently needed.

Disclosure of Potential Conflicts of Interest

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