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Review

Vitamin D, cod liver oil, sunshine, and phototherapy: Safe, effective and forgotten tools for treating and curing tuberculosis infections — A comprehensive review

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ABSTRACT

Tuberculosis remains an epidemic throughout the world, with over 2 billion people, or more than one third of the world's population, infected with TB. In 2015, there were an estimated 10.4 million new cases of tuberculosis, and 1.8 million deaths, making TB one of the top ten causes of death worldwide. Approximately 95% of new TB cases occur in developing countries, where the costs of treatment force many patients and their families into poverty. The United Nations and the World Health Organization are working to end this global epidemic. Historically, cod liver oil in the 1840′s, phototherapy in the 1890′s, sunshine in the 1890′s and 1930′s, oral vitamin D in doses of 100,000–150,000 international units a day the 1940′s, and injectable vitamin D in the 1940′s were all shown to be able to safely treat tuberculosis. However, for reasons that are unclear, these treatments are no longer being used to treat tuberculosis. We will review several reports that documented the clinical efficacy of these seemingly disparate treatments in treating tuberculosis. Taken together, however, these reports show the consistent efficacy of vitamin D in treating tuberculosis infections, regardless of whether the vitamin D was produced in the skin from the effects of phototherapy or sunshine, taken orally as a pill or in cod-liver oil, or put into solution and injected directly into the body. We will discuss how vitamin D, through its action as a steroid hormone that regulates gene transcription in cells and tissues throughout the body, enables the body to eradicate TB by stimulating the formation of a natural antibiotic in white blood cells, the mechanism of which was discovered in 2006. We will speculate as to why vitamin D, cod liver oil, sunshine, and phototherapy are no longer being used to treat tuberculosis, in spite of their proven efficacy in safely treating this disease dating back to the early 1800′s. In fact, in 1903 the Nobel Prize in Medicine or Physiology was awarded to a physician who was able to cure hundreds of cases of long-standing lupus vulgaris (cutaneous TB) with refracted light rays from an electric arc lamp. Vitamin D, cod liver oil, sunshine, and phototherapy have never been shown to lose their ability to safely eradicate tuberculosis infections, and deserve consideration to be re-examined as first-line treatments for tuberculosis. These treatments have the potential to help cost-effectively and safely end the global TB epidemic.

1. Introduction

Tuberculosis remains an epidemic throughout the world. It is estimated that over 2 billion people, or more than one third of the world's population, are infected with TB [1–3]. In 2015, there were an estimated 10.4 million new cases of tuberculosis, and 1.8 million deaths, making TB one of the top ten causes of death worldwide [3]. Both the United Nations and the World Health Organization are working to end the global tuberculosis epidemic, as approximately 95% of new TB cases occur in developing countries, where the costs of treatment force many patients and their families into poverty [1,3].

Antibiotics have been the mainstay of treatment for tuberculosis since the 1940′s. Streptomycin was discovered in 1943 [4,5], and reports soon followed showing it to be an effective treatment for curing tuberculosis infections [6,7]. In spite of the fact that resistance to antibiotics soon developed, antibiotic treatment of TB infections was so effective that in 1952 the Nobel Prize in Physiology or Medicine was awarded to Dr Selman Waksman for the discovery of streptomycin [8]. However, resistance to treatment with streptomycin and other antibiotics soon developed, and has remained a persistent problem since that time. Because of this, current treatment algorithms recommend starting with four drug regimens for patients infected with either

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pulmonary or miliary tuberculosis [9–11].

However, cod liver oil in the 1840′s [12], phototherapy in the 1890′s through the 1950′s [13–17], sunshine in the early 1900′s [18,19], oral vitamin D in the 1940′s [20–23], and injectable vitamin D in the 1940′s [24] were also independently shown to be able to safely cure tuberculosis infections, without concomitant antibiotic use. Interestingly, the 1903 Nobel Prize in Physiology or Medicine was also awarded to someone who developed a cure for TB. Dr Neils Ryberg Finsen was given the award after curing hundreds of cases of long-standing lupus vulgaris (cutaneous tuberculosis infections) by shining refracted light rays from an electric arc lamp onto the skin of infected patients in the 1890′s and early 1900′s [13–17]. He did this approximately 20 years before the discovery of vitamin D, and roughly 50 years prior to the discovery of antibiotics.

We will review reports that documented the clinical efficacy of these seemingly disparate treatment modalities in treating tuberculosis infections. We will then review a landmark study published in 2006 that ties them all together, by describing how vitamin D, through its action as a steroid hormone that regulates gene transcription in cells and tissues throughout the body, enables the body to eradicate TB by stimulating the formation of a natural antibiotic in white blood cells in response to their stimulation by tuberculosis antigens [25].

Taken together, these reports show the consistent ability and mechanism of action that enables vitamin D to treat tuberculosis infections, regardless of whether the vitamin D was produced in the skin from the effects of phototherapy or sunshine, taken orally as a pill or in cod-liver oil, or put into solution and injected directly into the body.

In order to better understand why these treatments aren't being used today, but deserve consideration to be re-examined as primary treatment modalities, we will also discuss:

a) reports on vitamin D toxicity from the 1930s and 1940s [26–28], and compare them to more contemporary reports [29–34];
b) data on the estimates of vitamin D production in the skin that were made in the 1970′s and 1980′s (and unknown in the 1940s), which range up to 25,000 IU a day [18,35–39];
c) several reports published in the same era describing the successful use of vitamin D in treating not only TB, but also asthma [40], rheumatoid arthritis [41], psoriasis [42], and rickets [43,44];
d) several recent vitamin D supplementation studies [45–49];
e) current controversies surrounding vitamin D supplementation involving the Institute of Medicine [50,51];
f) recent reports and reviews on the current use of vitamin D supplementation and testing in treating TB [52–62], and which appear to be using inadequate doses of vitamin D;
g) clinical trials from the 1980s and 1990s that showed both oral and topical vitamin D can safely control psoriasis [63–68]; and
h) clinical trials published in 2009 and 2010 that showed both sunshine and phototherapy can also safely control psoriasis [69–71].

2. Materials and methods

Beginning in 2009 a literature search was conducted by the authors looking for articles describing the treatment of human disease using cod liver oil, phototherapy, sunshine or vitamin D. The resulting discussion is taken from a review of several of these articles, with special focus on those that described the successful use of these varying modalities in treating and curing tuberculosis infections, which date from the 1840′s to the 1950′s [12–24].

It is notable that none of the references we are reviewing showing remarkable health benefits from the use of vitamin D, sunshine or phototherapy reported in the 1930s and 1940s for treating TB, asthma, rheumatoid arthritis and psoriasis, and again in the 1980s, 1990s and 2000s for treating psoriasis, were cited or discussed by the Institute of Medicine (IOM) in their 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D [50,51].

In their report, the IOM concluded that other than for certain measures of bone health, they could find no other convincing evidence for health benefits attributable to vitamin D. This appears to be a significant oversight on their part. The IOM also recommended avoiding sunshine to reduce the risk of developing skin cancer, assumed that all the vitamin D that a person requires comes from the diet, and stated that most people would be vitamin D sufficient by taking 600 International Units (IU) of vitamin D a day, along with a 25-hydroxyvitamin D blood level of 20 ng/ml. These recommendations also appear to be misguided.

3. Results

3.1. Tuberculosis and cod liver oil − 1840′s

The use of cod liver oil to treat and cure tuberculosis infections dates back to at least the early 1800s. In 1849, Dr CJB Williams, a London physician, wrote a report detailing his experience in treating over 400 patients suffering from pulmonary tuberculosis using cod liver oil [12]. He kept very good notes in 234 of the cases, which formed the basis of his report, in which he provides both a summary of his experience, as well as clinical descriptions of 11 individual cases.

In summary he stated that: "Out of this number, the oil disagreed, and was discontinued, in only nine instances. In nineteen, although taken, it appeared to do no good; whilst in the large proportion of 206 out of 234, its use was followed by marked and unequivocal improvement; this improvement varying in degree in different cases, from a temporary retardation of the progress of the disease, and a mitigation of distressing symptoms, up to a more or less complete restoration to apparent health."

He provided excellent descriptions of physical exam findings, thought processes as to when to use cod liver oil and how much to give, and individual patient responses to treatment. Many of his patients were cured, and marked improvement in their condition was often noted within a few days:

> "The most numerous examples of decided and lasting improvement, amounting to nearly 100, have occurred in patients in what is usually termed the second stage of the disease, in which the tuberculosis deposits begin to undergo the process of softening, the common physical signs being defective movement and breath-sound, with muco-crepitation and marked dullness below or above a clavicle, or above a scapula, and tubular breath and voice-sounds towards the root, or inner part of the apex of the same lung."

> "The effect of the Cod-liver oil in most of these cases was very remarkable. Even in a few days, the cough was mitigated, the expectoration diminished in quantity and opacity; the night-sweats ceased; the pulse became slower and of better volume; and the appetite, flesh, and strength were gradually improved."

At the end of the introduction, prior to describing the individual cases, he wrote a paragraph describing his experience in treating patients with advanced disease, which leaves little doubt as to the efficacy of the treatment:

> "The most striking instance of the beneficial operation of Cod-liver oil in phthisis, is to be found in cases in the third stage, even those far advanced, where consumption has not only excavated the lungs, but is rapidly wasting the whole body, with copious purulent expectoration, hectic night sweats, colliquative diarrhoea, and other elements of that destructive process by which, in a few weeks, the finest and fairest of the human family may be sunk to the grave. The power of staying the demon of destruction, sometimes displayed by the Cod-liver oil, is so marvellous, that I will attempt no general description, but will merely quote from my notebooks brief abstracts of a few specimen cases, that shall plead for themselves."

After reviewing in detail the remarkable clinical benefits that he observed in the 11 cases discussed in the report, he gave an interesting discussion of the possible "Mode of Operation of Cod-Liver Oil" in Section 2, and ended with a discussion of the "Preparation and Administration of the Cod-Liver Oil" in Section 3.

At the time of this publication, it would be another 73 years before vitamin D would be discovered, when it was isolated in 1922 from both cod liver oil and the skin of laboratory animals [18]. Yet the health benefits of cod-liver oil were widely recognized at that time. Cod liver oil is also a rich source of vitamin A, which has also been found to be important for normal cellular immune responses [72].

3.2. Tuberculosis and phototherapy – 1890's

In 1903, the Nobel Prize for Physiology or Medicine was awarded to Dr. Neils Finsen for his work in curing previously incurable cases of chronically disfiguring lupus vulgaris [13]. Lupus vulgaris is a cutaneous form of tuberculosis that may persist for years, and slowly erodes the skin, causing gross disfigurement.

The description of the disease given by Count Morner in his award ceremony speech honoring Dr Finsen was vivid: "Lupus vulgaris is, as we know, a form of tuberculosis, with localized lesions on the skin, especially that of the face, such as the nose, eyelids, lips and cheeks. The skin is gradually eroded, the face sometimes becomes dreadfully disfigured, and finally transforms patients into objects of repulsion. The chronic and progressive nature of this disease is particularly marked: it may remain active for ten years, twenty years, or even longer and, until now, it has proved resistant to all treatment. Even when patients had sufficient courage to persevere with these forms of treatment their hopes were dashed more often than not; rarely was a permanent improvement possible in this dreadful disease. Thus it was that Finsen's method was hailed as a benefit to humanity when his treatment of lupus gave results which can without exaggeration be described as brilliant."

Dr Finsen treated over 800 cases of lupus vulgaris between November 1895 and November 1901. He started off by using sunshine, but found that he got more consistent results with the use of refracted light rays from an electric arc lamp. The results he obtained were outstanding, as over 400 of the cases were completely cured: "In 50% of these cases the skin disease was cured, although in many of them the lesions were extensive and of long standing. In a great number of cases, so much time has elapsed since the recovery that one considers this as permanent. In the other 50% of these cases, in which a complete cure was not achieved, a partial cure or a considerable improvement was obtained in most cases. In only a very small number of cases, approximately 5% of all cases, treatment was unsuccessful or produced only temporary results. From the beginning of December 1901 until the end of October of this year, 300 further cases of lupus were treated." Count Morner also gave a detailed description of the technique that was used by Dr Finsen in his award ceremony speech.

In his biography, Dr Finsen gave insight into what led to his discovery [14]. He had become fascinated by the effect of sunshine on health, and knew that the sun did something to promote good health, probably on the blood, but was not sure exactly how the sun exerted its effects: "My disease has played a very great role for my whole development… The disease was responsible for my starting investigations on light: I suffered from anemia and tiredness, and since I lived in a house facing the north, I began to believe that I might be helped if I received more sun. I therefore spent as much time as possible in its rays. As an enthusiastic medical man I was of course interested to know *what benefit* the sun really gave. I considered it from the physiological point of view but got no answer. I drew the conclusion that I was right and the physiology wrong. From this time (about 1888) I collected all possible observations about animals seeking the sun, and my conviction that the sun had a useful and important effect on the organism (especially the blood?) became stronger and stronger. What this useful effect really was, I could not find; I have been working for this goal ever since but have not been able to find exactly what I have been seeking, though we have gone somewhat forward."

Unfortunately, Dr Finsen was unable to be at the award ceremony due to failing health, and died in 1904 at the age of 44 from Pick's disease. It would be another 18 years before vitamin D would be discovered in 1922. However, the medical community recognized the significance of his work, and adopted his method of treating lupus vulgaris. Reports verifying its efficacy in treating this disease appeared in the literature for several decades [15–17]. Unfortunately, its use in treating TB fell out of favor in part due to the discovery of the antibiotic streptomycin in the 1940's as previously discussed [4–7], and for which Dr Selman Waksman received the Nobel Prize for Physiology and Medicine in 1952 [8].

3.3. Tuberculosis and sunshine – 1930's

In a review on vitamin D published in 2007 [18], the authors noted that for many years sunshine was recognized as the only known cure for tuberculosis. No one knew exactly why it happened, but the observation had been made that when people suffering from tuberculosis were sent to sunny locations and exposed to sunshine, the disease was often cured. No references relating to this were cited in the article. However, this startling fact started us on an intensive search of the literature to find evidence documenting this assertion, and ultimately led us to the discovery of the articles that we are discussing in this review.

Interestingly, Hippocrates (460 B.C.–375 B.C.), who is widely considered to be the father of Western medicine, is thought to have recognized the healing power of sunlight (heliotherapy) centuries ago, and encouraged its use to treat a number of diseases.

In 1937, a report appeared detailing the beneficial effects of climate on outcomes in tuberculosis [19]. The potential benefits of temperature, humidity, air movement, sunshine, altitude, and rainfall in the treatment of TB were discussed. The discussion of sunshine is particularly interesting, and is in sharp contrast to the current opinion of the IOM [50,51], but is very similar to the view previously expressed by Dr Finsen:

> "Besides its mental effects, sunshine has many physiological actions. Sunlight is a good general tonic; it strengthens the skin, aids the digestion, increases the haemoglobin content of the red blood cells and improves the musculature. Sunlight also increases the bactericidal powers of the blood by increasing the number of white blood cells and improving their power of digesting disease-producing germs. For this reason a person taking sunbaths usually acquires increased resistance to intercurrent infections, such as colds. In certain kinds of tuberculosis such as tuberculosis of the skin, glands, or bones, heliotherapy is the ideal treatment. For pulmonary tuberculosis direct sunlight is not indicated until the disease has reached a stationary or very chronic stage where a moderate amount of stimulation is required. However, all cases of tuberculosis are generally benefited by the slight stimulation obtained from daily breathing sun-saturated air."

Actuarial data was also presented in the report, showing that outcomes in patients suffering from tuberculosis varied significantly in different parts of the country. The lowest death rates were observed in states in the Rocky Mountain region, which had significantly more hours of sunshine, less rainfall, and were at a significantly higher altitude than in the high death rate states:

> "The conclusion reached by the statisticians was that 'The remarkably low tuberculosis death rate for the Rocky Mountain States seems to be mainly accounted for on the basis of uniquely favorable climatic conditions.' From an unbiased study of all available evidence one must, therefore, conclude that a favorable climate is an asset in the treatment of tuberculosis."

It was known at that time that "the intensity of sunlight was

heightened as the elevation is increased," which likely allowed for more efficient production of vitamin D in the skin. The author concludes with a quote from one of his colleagues: "As Dr. Shurley once said: 'In the treatment of tuberculosis a cool, dry, high altitude with the greatest number of sunny days adds much to the percentage of recovery' in patients suffering from tuberculosis."

In stark contrast, while acknowledging that vitamin D is made in the skin from exposure to sunshine, in 2011 the IOM recommended avoiding the sun due to fears of developing skin cancer, did not acknowledge or refute current estimates that the skin will make up to 25,000 IU of vitamin D a day with adequate sun exposure [18,35–39], assumed that all the vitamin D a person needs comes from the diet, and stated that an intake of 600 IU a day (just 2.4% of 25,000 IU) is sufficient for the majority of the population, in making their recommendations for daily dietary intakes of vitamin D.

Considering it is now recognized that vitamin D is actually a steroid hormone that regulates gene transcription, and whose receptor has been found to have close to 3000 binding sites in a human cell line [73], implying that thousands of genes are dependent on vitamin D for their normal function, these recommendations appear inadequate. It should also be noted that sunshine and UV light have other effects that are independent of vitamin D, such as stimulating the production of melanin, nitric oxide, and beta-endorphins, and circadian rhythm control via regulation of melatonin and serotonin production [74] .

3.4. Tuberculosis and oral vitamin D – 1940's

In the 1940s, several reports were published providing specific details of safely curing multiple cases of lupus vulgaris using oral vitamin D as a single agent [20–23].

Daily doses of 100,000 IU to 150,000 IU of vitamin D2 for up to 6 months were typically used, and complete cures were safely obtained in most of the cases [20–23]. Serum calcium levels were reported, and were noted to be either normal, mildly elevated, or above 12 mg/dl, but patients still safely tolerated the treatment.

In 1945 Dr Dowling reported that "Serum calcium estimations in 12 of our cases after varying dosage and periods on the drug showed levels of between 10.1 and 10.8 mg per 100 c.c. in 6 cases; in 3 cases the levels were approximately 11 mg; and in 3 cases there was hypercalcemia, viz.12-6, 13-8, and 14–8 mg per 100 c.c. respectively." He also specifically noted that there was "no intolerance to the drug" in many of the cases described, and patients safely completed the course of therapy with complete resolution of the infection [20].

Dr Michelson recognized this in 1947 when he stated, "For the most part, administration of vitamin D in the doses which are recommended is perfectly safe, and the French authors comment on the lack of reactions. Dowling and Thomas noted signs of intolerance in 8 out of 38 patients mild in all but 1, all of whom were able to tolerate smaller doses without discomfort" [22].

Interestingly, estimates of the amount of vitamin D required to cause toxicity were quite high. Daily intake of vitamin D in doses in excess of 10,000 IU daily per pound of body-weight, or higher than 20,000 IU daily per kg of body weight were thought to be necessary to cause toxicity.

This was discussed in 1945 by Dr Dowling, who noted that, "From a review of the clinical results of many workers who have used Calciferol in diseases such as chronic arthritis, Bicknell and Prescott (1942) found that most patients tolerated Calciferol in doses of from 200,000 to 400,000 i.u. daily. They quote Steck and collaborators as stating, from extensive observations on over seven hundred patients, that few show toxic symptoms unless the dose exceeds 10,000 i.u. daily per pound of body-weight" [20].

In 1947 Dr Michelson made a similar observation: "Most drugs, including vitamin D, have a limit of dosage which if exceeded results in toxic and occasionally fatal reactions. The extreme toxicity of Viosterol as described in the older reports was probably due to the presence of an excess of toxisterol. In human beings and with modern methods of preparation, the incidence of intoxication is relatively low, and the toxic dose is about 20,000 international units per kilogram of body weight per day. This is from five to ten times greater than the doses that were employed in the present study" [22] (i.e.150,000 IU/day).

The realization was also made that oral vitamin D gave the same remarkable clinical results as seen with the use of cod liver oil, sunshine and phototherapy, and led to the conclusion that vitamin D was responsible for the benefits seen with cod liver oil, sunshine and phototherapy in treating tuberculosis infections.

This was noted by Dr Hellier in 1946: "It would now appear that we have constructed our wonderful light equipment, our Kromayer, our Finsen-Reyn lamps, merely for the sake of applying a dose of Calciferol to the skin, when it could have been given more readily by the mouth. I am particularly interested in the fact that the French discovered the same thing at about the same time. I asked Dr. Dowling if he knew of the French work, but the two were quite independent. The French method, called the method of Charpy, is described in the Annales de Dermatologie, for July 1945. The following results were obtained with vitamin D2: lupus vulgaris. 20 cases, 20 cures; vegetating tuberculosis, 1 case, 1 cure; lupus erythematosus, 5 cases, no cure, & c. The writer does not give-any reference to Charpy's original paper. I feel that this is a fundamental discovery" [21].

Previously, in 1945 Dr. J. E. M. Wigley had commented on the remarkable ability of vitamin D to cure TB: "I think we are all agreed that the results of this treatment, demonstrated by these six cases, is most striking; one might almost say epoch-making." [20].

By 1946, Dr Dowling had concluded that next step was in figuring out how vitamin D worked to cure tuberculosis infections: "These five cases, together with the six who were presented to the Section on November 15, and a considerable number of others which have responded in a similar way to the same treatment, can leave no room for doubt that Calciferol in adequate dosage will cure a substantial proportion of cases of lupus. The question that must interest us now is, how does it act? "[21]. The answer to this question, so poignantly raised by Dr Dowling above, was eventually answered 60 years later, and will be discussed shortly [25].

It was also recognized that treatment of TB with vitamin D was likely to be much more cost effective than other current treatments available at that time. In 1945, Dr. J.E.M. Wigley spoke to the cost effectiveness of using vitamin D to treat tuberculosis: 'I think not the least important aspect of this treatment is an economic one. Treatment of lupus by other methods, e.g. Finsen light, general U.V.L., etc., has always had the great disadvantage of being very costly, both in apparatus and staff required, and in the patient's time, including loss of earning capacity. I do not wish to say that we can now dispense with these methods of treatment, but if the response to Calciferol shows the continued, generally excellent results demonstrated today, a great advance will have been made in the method of dealing with this very serious social menace' [20].

To briefly summarize, several reports from the 1940s describe patients whose lupus vulgaris was safely cured by taking 100,000 IU to 150,000 IU a day of oral vitamin D for 3 to 6 months. Many of these patients did not appear to develop hypercalcemia during the course of their treatment, and those who did do not appear to have suffered to any significant degree over the time course of their treatment, and were able to complete the course of treatment, sometimes with slight dose reductions. In these patients, the benefits of treatment with vitamin D clearly outweighed the risks.

In 1947 Dr Michelson summarized this experience by stating: "Many points need clarification before this therapy can be fully accepted…. In the meantime, the administration of vitamin D to patients with cutaneous tuberculosis in a dosage of 150,000units daily constitutes, in our opinion, the most useful therapy available" [22].

3.5. Tuberculosis and injectable vitamin d − 1940's

In 1946 "Vitamin D − Its Bactericidal Action" was published, in which the author reported the results of successfully using vitamin D both in-vitro in treating tuberculosis grown in culture, and in-vivo in treating 6 patients with advanced pulmonary tuberculosis [24]. All 6 patients were extremely ill, had empyemas with complicating pneumothoraxes, had failed conservative treatments, and were very poor surgical risks.

In the clinical trial, concentrated solutions of vitamin D were injected intrapleurally once a week. One patient improved enough clinically after 3 months to have surgery for a previous rib resection, and dropped out of the study. Five of the patients continued the weekly injections for 8 to 9 months. The chest fluid was aspirated periodically and cultured for growth. The pus was noted to turn negative in 2 to 3 weeks in most of the patients, with an increased concentration of leucocytes noted. Of the remaining 5 patients, one turned negative after 8 months, but was doing poorly, and was considered a failure. The remaining four patients showed marked improvement clinically.

As noted by Dr Raab, "The most outstanding late result in the remaining four cases is that their collapsed lungs did re-expand. After the early conversion of the positive pus, all attempts to re-expand the lung failed. However, continuation of the vitamin D injection and infrequent aspirations brought about a spontaneous re-expansion which took 6 to nine months. ...All four patients showed a marked gain in weight." The clinical benefit observed in the four patients treated once weekly with intrapleural injections of vitamin D appears to be quite remarkable, and is consistent with the results discussed in the previous sections of this report.

The author also reported results on the in-vitro effect of vitamin D on the growth of other several other microorganisms present in the pleural fluid and empyema, and found it to be effective in killing these other microorganisms in addition to the tubercle bacilli, and concluded with the following statement:

> "SUMMARY: Vitamin D, activated ergosterol, is bactericidal to tubercle bacilli, proteus, bacillus aerogenes, staphylococci and non-hemolytic streptococci in vitro and in vivo."

3.6. How vitamin D works to cure tuberculosis infections − 2004–2006

The question asked by Dr Dowling in 1946 regarding the ability of vitamin D to kill TB, as to "…how does it act?" was eventually answered in the early 2000's.

In 2004 and 2005, it was reported by two different groups that 1,25-dihydroxyvitamin D3 (calcitriol), the active hormone form of vitamin D, directly regulates antimicrobial innate immune responses [75,76]. Calcitriol was found to induce antimicrobial gene expression in several human cell lines, resulting in the formation of cathelicidin antimicrobial peptide (Camp). This was shown to occur in isolated human keratinocytes, monocytes and neutrophils, and human cell lines, with activity against pathogens including pseudomonas aeruginosa [75], and in acute myeloid leukemia (AML), immortalized keratinocyte, and colon cancer cell lines, as well as normal human bone marrow (BM) − derived macrophages and fresh BM cells from two normal individuals and one AML patient [76].

Thus, the discovery was made that many different cells in the human body are programmed to produce an antibiotic by activating a vitamin D dependent gene in response to stimulation by calcitriol. This is important because as noted by Dr Gombart in 2006, "The innate immune system of mammals provides a rapid response to repel assaults from numerous infectious agents including bacteria, viruses, fungi, and parasites."

In 2006, a study involving tuberculosis proteins and white blood cells (wbcs) showed that Camp is also produced in wbcs following stimulation of toll-like receptors on the cell surface by tuberculosis antigens [25].

In this study, several processes involving vitamin D were shown to occur inside the wbcs after binding of the tuberculosis proteins to toll-like receptors on the cell surface of the wbcs. Two genes were initially activated inside the wbcs. One gene was shown to make multiple copies of the vitamin D receptor (VDR), and the other gene was shown to make multiple copies of the enzyme 25-hydroxyvitamin D 1-alpha hydroxylase, which is the enzyme that converts circulating 25OHD into 1,25-dihydroxyvitamin D3 (calcitriol), the active hormone form of vitamin D3.

Calcitriol was then produced inside the cells, and the gene product was discovered to be Camp. Camp was found to be capable of killing mycobacterium tuberculosis, and is totally dependent on vitamin D to be produced [77].

This discovery explains why vitamin D3 was able to cure the tuberculosis infections that was observed and documented decades ago in the pre-antibiotic era using either cod liver oil, phototherapy, sunshine, oral vitamin D, or injectable solutions of vitamin D. It also explains why TB infections continue unabated in a state of vitamin D deficiency.

In a state of vitamin D deficiency, the body is unable to sufficiently activate the gene that makes Camp. As a result, inadequate amounts of antibiotic are produced, and the mycobacterium is unable to be killed. In a state of vitamin D sufficiency, the gene is adequately activated, and Camp is made in sufficient quantities to eradicate the infection. With all 5 therapies, the common endpoint is the patient is taken from a state of vitamin D deficiency to a state of vitamin D sufficiency. This then provides the immune system with sufficient quantities of the substrate that it needs (i.e. calcitriol, the active hormone form of vitamin D3) to turn on the gene inside white blood cells that produces cathelicidin, enabling the body to fight the infection.

The reason cod liver oil works is because it is a very concentrated food source of vitamin D3. Phototherapy and sunshine work because both are able to cause the production of vitamin D3 in the skin from the precursor molecule 7-dehyrocholesterol [18,35–39].

It's the sufficiency of vitamin D3 in the blood that matters, not how it was formed (e.g. via sunshine or phototherapy) or delivered into the body (e.g. via ingestion of cod liver oil, a vitamin D pill, or liquid solution of vitamin D, or injection of a liquid solution of vitamin D into the body).

3.7. Why the use of oral vitamin D fell out of favor for treating TB in the 1940s:

As mentioned earlier, during this era, in addition to using oral vitamin D to treat TB, vitamin D was also shown to be safe and effective in treating several other diseases, including asthma, rheumatoid arthritis, rickets and psoriasis. Daily oral doses of vitamin D ranging from 60,000 to 300,000 IU produced remarkable clinical benefits in the treatment of asthma [40], doses ranging from 200,000 IU to 600,000 IU produced remarkable clinical benefits in the treatment of rheumatoid arthritis [41], and doses of around 20,000 IU a day were shown to be extremely effective in clearing the skin plaques in patients with psoriasis, even in patients with 10 to 30 year-long histories of previously uncontrolled psoriasis [42].

However, hypercalcemia and its attendant symptoms began to occur with prolonged use of these high doses, with serum calcium levels ranging from 12 to 20 mg/dl seen in some, but not all patients. Although hypercalcemia was never clearly established as the cause, a small percentage of these cases were ultimately associated with several deaths [26–28]. To illustrate this point, one of last reported deaths suspected to be related to vitamin D toxicity during that era that we are aware of occurred in 1945 in a woman who took 150,000 IU to 200,000 IU of vitamin D a day for 18 months, and who had serum calcium levels ranging from 13 to 14.7mg% [27]. Detailed autopsy results were reported, but the exact cause of death was never ascertained. However, a close review of the report suggests that her death did not appear to be

caused by complications related to vitamin D induced hypercalcemia.

Unfortunately, this association caused the use of what was even then recognized to be very high doses of oral vitamin D to fall out of favor, and the recommended daily dosing was reduced to much smaller doses in the range of 400 to 600 IU a day, which were effective for treating rickets, but were ineffective in treating asthma, RA, psoriasis and TB. And as discussed earlier, antibiotics with anti-tuberculosis activity were also discovered in the 1940′s, and soon became the mainstay of treatment.

In 1946 Dr Bicknell pointed out that "There has been very little work done in England on the toxicity of Calciferol; it would be of value and easy, now that large doses are being given, to check unconfirmed reports about the premonitory symptoms of poisoning–such as acute tenderness of the back of the head. Presumably some cases of lupus have vascular degeneration, coronary disease or nephritis: in all these conditions Calciferol is especially dangerous, so it is important to determine the minimum dose which is effective in curing lupus. It might be possible to give Calciferol in an ointment, thereby securing a higher concentration in the lesion and a less high concentration in the arteries" [21].

However, practical methods of measuring vitamin D in the blood weren't developed until the 1970′s [78,79], so the blood levels of 25OHD associated with the hypercalcemia were not known. And it wouldn't be until the late 1970′s and early 1980′s that estimates of the amount of vitamin D made in the skin from adequate sun exposure would be made, which were in the range of 8000 to 25,000 IU a day [18,35–39].

Had scientists known these facts during that era, perhaps they would have followed Dr Bicknell's advice and tried to "determine the minimum dose which is effective in curing" not only TB, but also in controlling asthma, RA and psoriasis. This still needs to be done.

3.8. Current use of cod liver oil, sunshine, phototherapy and vitamin D in treating tuberculosis infections

Vitamin D deficiency has been shown to be prevalent in patients suffering from TB around the world, even in sun rich locations [52–62]. However, none of the safe and effective treatment modalities that we have discussed in this review, i.e. cod liver oil, sunshine, phototherapy or vitamin D, are currently being used as single agents to treat TB [9–11,60–62].

Vitamin D is being used to treat TB, but only in combination with antibiotics, and the results of its treatment efficacy have been mixed. However, the explanation may be due to a dose response issue. The doses of vitamin D used in these reports appear to be grossly inadequate, as they are neither in the range of vitamin D estimated to be produced in the skin from sun exposure, nor anywhere close to the amounts shown to be safe and effective in curing TB in the 1940′s. As Dr Dowling noted in 1946, "These five cases, … can leave no room for doubt that Calciferol in adequate dosage will cure a substantial proportion of cases of lupus."

4. Discussion

Vitamin D is currently one of the most controversial and misunderstood topics in medicine. And as the discussion of the literature presented in this review shows, an exceedingly important one. Contrary to the assertions made by the IOM in their 2011 report regarding the paucity of health benefits of vitamin D and sunshine as discussed earlier [50,51], there are actually many reports in the literature that provide clear and convincing evidence of the clinical efficacy and safety of both vitamin D and sunshine in treating a number of diseases, beyond just certain measures of bone health.

Tuberculosis, which has been a scourge to mankind for centuries and remains so today, is just one of several diseases that were missed by the IOM. And if we are ever going to win the fight against tuberculosis, we need to use all the tools that we have at our disposal, and this would include the use of cod-liver oil, sunshine, phototherapy and vitamin D. The ability of cod-liver oil, a highly concentrated food source of vitamin D, to cure TB infections was documented in 1849 in the London Journal of Medicine [12]. Half a century later both sunshine and phototherapy were being used cure TB, and the Nobel Prize in Medicine awarded to Dr Neils Ryberg-Finsen in 1903 in recognition of his success in curing hundreds of cases of lupus vulgaris using refracted light rays from an electric arc lamp. It was quite a remarkable accomplishment, and is a very fascinating story [13,14].

The Finsen method of phototherapy soon became the standard of care for treating tuberculosis for several decades [14–17]. Vitamin D was eventually discovered in 1922, when it was isolated from the skin of laboratory animals and also from cod liver oil [18]. Sanatoriums were also developed during this era after it was recognized that sunshine could be used to treat patients with tuberculosis, and were used successfully in curing many people of TB [19].

Soon after the discovery of vitamin D in 1922, physicians realized that the mechanism of action of cod liver oil, sunshine and phototherapy in curing tuberculosis infections was likely due to the formation of vitamin D in the skin [21]. Clinical trials using oral formulations of vitamin D as a single agent in doses of 100,000 IU to 150,000 IU a day for several months were then shown in the 1940′s to be safe and effective treatments for curing TB infections, thus proving the hypothesis [20–24].

Eventually, one hundred and three years after Dr Finsen received the Nobel Prize for curing TB with phototherapy, the mechanism of action by which vitamin D works to cure TB infections was discovered [25], and Finsen's hypothesis that sunshine did something to the blood to improve health was proven. In this 2006 report, it was shown that vitamin D is the gene switch that turns on a gene in wbcs that makes the antibiotic cathelicidin, which then enables the body to cure tuberculosis infections. Cathelicidin is made in multiple cells in the body, and its production is under the control of vitamin D [75–77].

Interestingly, cod liver oil, sunshine and vitamin D were also shown years ago to be able to cure rickets, the bone deforming disease of childhood [43,44]. Different genes are undoubtedly activated by vitamin D in curing this disease.

However, it wasn't until the late 1960′s that scientists started deciphering the metabolic pathway of vitamin D, and realized that it actually exists in several different forms in the body, and ultimately functions as a seco-steroid hormone [80], that controls the transcription of thousands of different genes in cells and tissues throughout the body [73]. Practical methods of measuring the different forms of vitamin D in the blood were not developed until the 1970′s [78,79]. Soon afterwards, in the late 1970's and early 1980′s, estimates of the amount of vitamin D that is made in the skin from adequate sun exposure on a daily basis were made, and these amounts were shown to be in the range of 10,000 International units (IU) to 25,000 IU [35–39].

If these estimates of vitamin D production are accurate, then intuitively it would suggest that taking daily doses of vitamin D3 in this range would likely be safe to do [29], especially in light of the fact that it has been determined that the body will not overproduce the amount of vitamin D3 that it needs from sun exposure [36]. As discussed earlier, for unknown reasons, these estimates of vitamin D production in the skin were not directly discussed, acknowledged, refuted, or endorsed anywhere in the 2011 IOM report [50,51], although two of these references [35,37] were cited in the report. This, along with other conclusions and recommendations made by the IOM, has served to create quite a controversy in the fields of vitamin D research and public health.

The safety of taking daily doses of vitamin D in the range made in the skin by sunshine, or even higher, has been born out in several reports and reviews. These include not only the studies discussed earlier from the 1930s and 1940s with tuberculosis, asthma, RA and psoriasis that utilized much higher doses of oral vitamin D, but also several more

recent publications.

In the 1980s and 1990s, several reports were published attesting to the safety and efficacy of both oral and topical vitamin D in treating patients suffering from psoriasis [63–68], confirming the results reported several decades earlier by Dr Krafka [42]. In these clinical trials the authors used oral formulations of either 1-hydroxyvitamin D3, or 1,25-dihydroxyvitamin D3.

These reports were then followed by several reports documenting the clinical efficacy and safety of both sunshine and phototherapy in treating psoriasis from between 2008 and 2010 [69–71,81,82]. In all of these reports, baseline 25OHD blood levels above 20 ng/ml were commonly reported, yet the patients still responded to treatment with either vitamin D or UVB radiation.

So not only have sunshine and phototherapy been shown to cure tuberculosis infections, both have been shown in recent clinical trials to be safe and effective treatments for controlling psoriasis [69–71], are both recommended as treatments for psoriasis by the National Psoriasis Foundation [81], while phototherapy is recommended by the American Academy of Dermatology (AAD) [82].

In regards to the safety of treatment with phototherapy and the risk of cancer, the AAD stated, “Photoaging is a long-term side effect, and features of dermatoheliosis including wrinkling, lentigines, and telangiectasias may occur. Photocarcinogenesis is a potential adverse effect of UVB phototherapy; however, numerous studies have failed to show such an effect in patients with psoriasis after UVB therapy” [82].

Unfortunately, all of these reports on psoriasis were missed by the IOM, as a word search revealed that the word psoriasis does not appear one time in their 2011 report. However, psoriasis now represents the third disease that we discovered in our review for which both vitamin D, sunshine and phototherapy have been shown to be safe and effective treatments, the others being TB and rickets.

In 2003, a clinical trial attesting to the safety of daily oral dosing with either 5000 IU or 10,000 IU a day of vitamin D3 was reported [45]. This study was conducted in healthy volunteers over a 5-month period in the wintertime in Omaha, Nebraska. No adverse events were associated with the intake of vitamin D3 in these doses, and no cases of hypercalcemia occurred. The highest mean 25OHD blood levels were 64 ng/ml and 88 ng/ml.

In 2007, a group of physicians reviewed the world’s literature on vitamin D to generate a risk assessment for vitamin D toxicity [31]. Their stated goal was: “To apply the risk assessment methodology used by the Food and Nutrition Board (FNB) to derive a revised safe Tolerable Upper Intake Level (UL) for vitamin D. New data continue to emerge regarding the health benefits of vitamin D beyond its role in bone. The intakes associated with those benefits suggest a need for levels of supplementation, food fortification, or both that are higher than the current levels.”

After thorough review of the available literature, discussed in detail in their report, they concluded that the then UL of 2000 IU was too restrictive, and should be changed to 10,000 IU. They also noted that: “No consistent and reproducible hypercalcemia or any other adverse effect from vitamin D has occurred in well-conducted clinical trials at intakes up to 1250 ug/d (50,000 IU/d). The limited duration, size, or lack of other appropriate design characteristics prevent the selection of intakes of 1250, 450, or 321 ug vitamin D/d as a NOAEL that would warrant a high level of confidence. The strong design characteristics and absence of adverse effects in the clinical trials at 250 ug D/d [30,35] and the absence of adverse effects at higher as well as lower doses justify the selection of 250 ug (10,000 IU) vitamin D as the NOAEL for the general healthy population.” The NOAEL is the no-observed adverse-effect level.

These last 2 reports were considered and discussed by the IOM in their 2011 report, but for various reasons the committee decided to take a much more conservative approach, and recommended a revised UL of only 4000 IU. This is also in contrast with the recent Clinical Practice Guideline on the Evaluation, Treatment and Prevention of vitamin D deficiency published by the Endocrine Society in 2011, which adopted the UL of 10,000 IU [39].

Several additional reports published since the 2011 IOM report provide further evidence that daily intake of vitamin D in doses ranging from 10,000 IU to 50,000 are safe for prolonged periods of time, ranging from 50,000 IU/day for 9 months [47], to 10,000 to 60,000 IU/day for up to 6 years [46,48,49]. Serum levels of 25OHD above the currently accepted upper limit of normal of 100 ng/ml were also reported in these studies, and were over 200 ng/ml in one [48]. There were no reported cases of hypercalcemia or any other adverse events related to vitamin D. In fact, not only were no adverse events reported, but one patient with advanced pancreatic cancer was noted to have striking disease stabilization over the nine months, which is what prompted the report to be published [47], and another reported marked clinical improvement in the control of his asthma, which has since lasted for several years [48].

In addition, several recent reports on accidental overdosing with vitamin D give further insight into the safety and toxicity of vitamin D.

For example, a remarkable report from 2011 on accidental overdosing with massive doses of vitamin D suggests that 25OHD blood levels up to 400 ng/ml may be safe [33]. In this report, two patients accidentally ingested massive doses of vitamin D on a daily basis due to manufacturing and labeling errors. One patient took over 1.8million IU’s a day for 2 months, and the second took over 900,000 IU’s a day for 1 month. Both became ill from hypercalcemia, and had peak 25OHD blood levels of 1220 ng/ml and 645 ng/ml, respectively. However, both patients recovered uneventfully after the vitamin D3 was stopped, although they did require varying amounts of supportive care. Interestingly, both were noted to become asymptomatic and to have normal calcium blood levels after the 25OHD level decreased below 400 ng/ml.

Also, in 2016 a retrospective report from the National Poison Data System (NPDS) reviewed 25,397 calls to the NPDS about overdoses of vitamin D between the years 2000 to 2014 [34]. The mean number of cases increased from 196 between the years 2000 to 2005, to 4535 between the years 2005 to 2014. During that 15-year period there no deaths, and serious medical outcomes were infrequent. In contrast, during that same time, there were about three thousand deaths due Tylenol overdoses, suggesting that vitamin D is actually much safer than Tylenol.

However, the pendulum has swung from the use of supra-physiological doses of vitamin D in the 1930′s and 1940′s, which showed remarkable clinical benefits, to the use of sub-optimal, sub-physiological doses of vitamin D that have commonly been reported in clinical trials conducted in the last 30 years (i.e. 200 IU, 400 IU, 600 IU, 800 IU, 1000 IU, 2000 IU, 4000 IU), and which have shown variable clinical benefits.

It would be very interesting to see if the use of physiologic daily oral doses of vitamin D3, in the range of amounts estimated to be produced in the skin on a daily basis from sunshine with adequate exposure to the skin, would have the same clinical benefit as obtained with the supra-physiological doses used in the 1930s and 1940s, without any attendant hypercalcemia or side effects. To date, clinical trials using physiological doses of oral vitamin D3 have not been done in TB, asthma, psoriasis, or RA.

The lack of efficacy of vitamin D seen in recent reports of its use in treating TB appears to be a dose response problem. We hypothesize that daily oral doses of vitamin D3 in the range of 10,000–50,000 IU a day would likely be able to safely cure a significant percentage of TB infections, just as the larger doses of 100,000 IU–150,000 IU of vitamin D were shown to do in the 1940s. It would still be of great interest today to determine the minimum dose of oral vitamin D needed to cure TB, as Dr Bicknell stated in 1946 [21], as well as to verify that treatment of TB with oral vitamin D as a single agent is still effective.

5. Conclusion

TB remains a significant public health problem, estimated to affect nearly one third of the world's population. In 2015, there were an estimated 10.4 million new cases of tuberculosis, and 1.8 million deaths, making TB one of the top ten causes of death worldwide. This is in spite of the fact that two physicians, from two different eras, were each awarded the Nobel Prize for Physiology or Medicine for finding two different cures for the disease.

Correction of vitamin D deficiency has been shown to be able to safely cure tuberculosis infections, regardless of whether the vitamin D deficiency was corrected by ingestion of 2 to 3 teaspoons of cod-liver oil (a concentrated food source of vitamin D) daily for several months, formation in the skin vitamin D3 by the action of UVB radiation on 7-dehydrocholesterol, ingestion vitamin D daily by mouth in amounts of 50,000 IU two or three times a day for 3 to 6 few months, or injection of concentrated solutions of vitamin D directly into the body (e.g. into the pleural cavity).

These treatment modalities fell out of favor with the discovery of antibiotics with anti-tuberculosis activity in the 1940s, and also due to concerns related to vitamin D-induced hypercalcemia that developed during that era, when doses of vitamin D much higher than those estimated to be produced from sun exposure to the skin were used. However, resistance to antibiotics also soon developed, and remains a significant problem, necessitating the use of costly 2 and 4 drug treatment regimens.

Vitamin D, cod liver oil, sunshine, and phototherapy deserve consideration to be re-examined as first-line treatments for tuberculosis. As vitamin D deficiency has been shown to be common in patients infected with TB throughout the world, correction of vitamin D deficiency by any of these means should still be an effective treatment to eradicate tuberculosis infections, as we now understand how vitamin D works to cure tuberculosis infections.

Our review of the literature on vitamin D clinical trials, dosing, safety and toxicity studies suggests that such studies are likely to be safe and effective. Due to the scope of the current tuberculosis epidemic, any additional safe and effective treatments that could be developed for curing tuberculosis infections would be of great benefit to mankind. Reevaluation of these proven but forgotten treatments has the potential to go a long way toward helping to safely and cost-effectively end the global TB epidemic.

Conflicts of interest

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