

Vitamin D supplementation in patients with active or latent tuberculosis

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[D-vitamin supplementering hos patienter med aktiv eller latent tuberkulos]

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Statement from the Regional HTA-centrum 2012-03-28

Utlåtande från HTA-centrum 2012-03-28

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HTA-centrum of Region Västra Götaland - presentation

Summary of the Health Technology Assessment

Method and patient group

Patient value of vitamin D supplementation in patients with active or latent tuberculosis (TB).

Question at issue

Does vitamin D supplementation, as compared to no treatment or placebo, reduce mortality, slow progression of disease, reduce disease susceptibility or increase the quality of life in patients with active or latent TB infection?

PICO

P= Patients, I= Intervention, C= Comparison, O=Outcome

P1= Patients with active TB, with or without treatment.

P2= Patients with latent TB, with or without treatment.

I = Vitamin D supplementation, with or without calcium supplementation.

C = Placebo, no treatment.

O1= Mortality.

Progression of disease.

Health-related quality of life.

Adverse events.

O2= Mortality.

Susceptibility to disease/development of disease.

Health-related quality of life.

Adverse events.

Studied risks and benefits for patients of the new health technology

PICO 1: Patients with Active TB

Four randomised controlled trials (RCTs) and nine case series fulfilled the inclusion criteria.

No significant effect of vitamin D supplementation was seen on mortality in patients with active TB in the two RCTs which had this as an outcome. Low quality of evidence (GRADE ⊕⊕○○).

No significant advantages regarding progression of disease in patients with active TB were found in the two RCTs of high quality. One low-quality RCT reported a significantly reduced time to sputum smear conversion in the vitamin D group. The fourth study claimed to have found an effect on symptoms, but the presentation of the results was so vague that it was impossible to draw any conclusions from that study. Very low quality of evidence (GRADE ⊕○○○).

There were no studies with the outcome health-related quality of life on the effects of vitamin D supplementation in patients with active TB.

There were very few adverse events.

PICO 2: Patients with latent TB

No articles based on this patient group were identified.

Complications and side effects

With current substitution dosage (1600 IE/day), side effects were minimal or absent.

Ethical aspects

There are few risks with medically indicated vitamin D supplementation, as long as overdosage is avoided. Refraining from treatment due to lack of solid scientific evidence for a beneficial effect on TB generates some ethical problems. Irrespective of TB status, serum levels of less than 30 nmol/l of 25-OH-vitamin D (25OHD) are associated with rachitis in children and osteomalacia in adults and there are also studies indicating increased overall mortality in persons with 25OHD < 30nmol/l. A very large proportion of the patients seen in our departments belong to this category. It therefore seems unethical not to test for and correct deficiencies with 25OHD levels below 30-50 nmol/l, even in the absence of solid evidence for a specific effect on TB.

Economical aspects

Testing for vitamin D deficiency is relatively inexpensive, but may involve many individuals leading to considerable costs, especially in the primary health care sector.

Conclusion

Vitamin D supplementation has no significant effect on mortality (low quality of evidence, GRADE ⊕⊕○○), or disease progression in patients with active TB (very low quality of evidence, GRADE ⊕○○○). No articles were identified studying the effect of vitamin D supplementation on quality of life in patients with active TB. Neither was any studies identified with these outcomes in patients with latent TB. In patients with very low vitamin D levels (25OHD levels below 30-50 nmol/L), treatment is probably indicated irrespective of TB status but this aspect was not analysed in the current HTA report.

The assessed health technology or method

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1b The question was posed by:

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Conflicts of interest for the proposer or any of the participants in the work group?

No competing interests declared.

Disease/disorder of Interest and Present Treatment

2a Disease/disorder of interest and its degree of severity

Infection caused by *Mycobacterium tuberculosis* remains a major threat to global health. The most common manifestation is lung tuberculosis (TB), but almost any organ of the body can be affected. If left untreated, the mortality in TB is very high. Latent TB is present when a patient is infected with *M. tuberculosis*, but does not have clinically active disease.

Due to migration, poverty, the HIV/AIDS epidemic, and multi-drug-resistance, the worldwide incidence of TB increased during the last years of the twentieth century, and reached a peak in 2002 (WHO, 2011). Since then the incidence has fallen by approximately one percent per year, and since 2006 the absolute number of new cases has declined. Nevertheless, one third of the world's population is estimated to have latent TB, and almost nine million individuals develop active TB every year, resulting in 1.5 million deaths per year (WHO, 2011).

Degree of severity

- Risk of premature death
- Risk of permanent illness or damage, or reduced quality of life
- Risk of disability and health-related quality of life

2b Prevalence and incidence of the disease/disorder in Sweden

In nineteenth century Sweden, TB was one of the leading causes of death. Until 2002, the incidence and prevalence of TB decreased dramatically due to better living conditions and the introduction of effective antibiotics. However, in 2002 the incidence started to increase again with 595 cases reported to the Swedish Institute for Communicable Disease Control in 2011 (SMI, 2012). The recent increase is solely due to immigration from countries with a high incidence and prevalence of TB, while TB in the native population continues to decrease. In VGR 110 cases of TB were reported in 2010 as well as in 2011, which is a 34% increase compared to 2009 (Department of Communicable Disease Control Region Västra Götaland, 2012). Eighty-five percent were infected abroad, with African countries accounting for 55% of the total number of cases. Fifteen patients were under 18 years old.

Currently there is no available data on incidence or prevalence of latent TB in Region Västra Götaland (VGR). In a study of 600 unvaccinated medical students born in Sweden, about one percent were diagnosed with latent TB based on the tuberculin skin test (Fjällbrant *et al.*, 2010). Since the population in VGR has a higher median age and many residents are born outside Sweden, the incidence is expected to be higher as compared to the group studied by Fjällbrant *et al.* (2010). Also, the number of patients that are referred to the clinics in VGR due to a positive TB test result has increased during the past few years, mainly due to immigration from high incidence countries.

Intake of dietary vitamin D from fish, meat, and enriched dairy products contributes to vitamin D levels, but sunlight is the most important source. Active vitamin D is formed by sunlight on the skin, and individuals with dark skin require much more sun

exposure to synthesise sufficient amounts. A large part of the TB patients in VGR originate from the Horn of Africa and have an innate dark skin. In addition, it is common to cover large parts of the body within this group, especially among women.

2c Present treatment of the disease/disorder in the outpatient setting/ in-patient setting

The standard treatment regimen includes rifampicin and isoniazid for six months, with the addition of pyrazinamide during the first two months. If the bacterial sensitivity testing is not completed when the treatment is initiated, ethambutol is added until the strain has been found to be fully sensitive, or if sensitivity is not ensured, administered for two months. Depending on drug resistance, clinical course and location of the infection, treatment may be prolonged and/or modified.

Latent TB is treated when the risk of developing active disease is believed to be high and good treatment adherence is expected. Adults are treated with isoniazid for six to nine months, whereas children are sometimes treated with a combination of isoniazid and rifampicin for three months.

2d Number of patients per year who undergo current treatment regimen

One hundred and nine patients started treatment against active TB in VGR during 2011. Thirty to 50 patients are treated for latent TB every year at the Pediatric Department at Sahlgrenska University Hospital. In 2011, approximately ten patients were treated at the Department of Infectious Diseases, and 40-45 patients at the Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital.

2e The normal pathway of a patient through the health care system

Pulmonary TB is the most common form of TB in VGR, and is usually treated at the Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Göteborg, or at one of the three Infectious Diseases Clinics in Borås, Skövde and Trollhättan. Extrapulmonary TB is treated at the Department of Infectious Diseases, Sahlgrenska University Hospital, Göteborg, or at one of the other three Infectious Diseases Clinics. The Paediatric Departments (Borås, Göteborg, Skövde, Trollhättan) are responsible for paediatric patients with TB.

Once treatment has started the medical staff closely monitor the intake of medication, as well as clinical and laboratory parameters. The DOTS-regimen (directly observed treatment, short course) is used whenever necessary, but more often a modified DOTS-regimen is used.

2f Actual wait time in days for medical assessment /treatment

Patients with suspected, possibly contagious, pulmonary TB are usually referred to a hospital immediately, or within a few days. Depending on the patient's condition and the degree of possible contagiousness, admission and isolation may be necessary until sputum smears for acid-fast bacilli have been analysed. Patients with positive sputum smears are sometimes isolated during the first two weeks of treatment, before discharge. When extra-pulmonary TB is suspected, investigation is usually started within one or two weeks from referral. The location of the infection and the patient's condition determine whether the patient is hospitalised, or if work-up prior to the initiation of treatment can be done at a TB outpatient clinic. Sometimes the diagnosis is delayed because one or more physicians overlook the possibility of TB.

3a Name/description of the health technology at issue

Lack of vitamin D is known to contribute to rachitis and ostemalacia. Lately it has also been suggested to play a role in the development of several other diseases including TB (Thatcher and Clarke, 2011). There are indeed some theoretical arguments for a role of vitamin D in the defense against TB. The active form of vitamin D (1-alpha 25-hydroxyvitamin D) induces activity against TB bacteria in monocytes (Rook *et al.*, 1986), and macrophages (Crowle *et al.*, 1987) *in vitro*. Several mechanisms of action have been proposed, including induction of oxidative burst (Sly *et al.*, 2001), and promotion of phagolysosome fusion in macrophages (Hmama *et al.*, 2004). Vitamin D receptor mediated modulation of the immune response has also been described (Rockett *et al.*, 1998), as well as release of an antimicrobial peptide (cathelicidin) with an effect against intracellular *M tuberculosis* (Liu *et al.*, 2006).

Another indirect argument for an association between vitamin D levels and TB is the parallel seasonal variation in vitamin D status and TB incidence that has been observed (Fares, 2011; Visser *et al.*, 2012). In primary infection and reinfection, but not in reactivation, this phenomenon might theoretically reflect an increased risk of transmission of TB during winter months (Fares, 2011). Two recent studies used the tuberculin skin test to evaluate if vitamin D levels are related to the risk of TB infection. An observational case-control study from Spain of recent TB contacts claimed that a sufficient serum vitamin D level protected against tuberculin skin test conversion, and that the mean of serum level vitamin D in cases that converted was lower than in controls (Arnedo-Pena *et al.*, 2011). Similarly, in an RCT with vitamin D supplementation of 800 IU/d for 6 months in 120 Mongolian children (Ganmaa *et al.*, 2012), a trend was seen towards fewer tuberculin skin test conversions in the vitamin D group. These results suggest that sufficient vitamin D levels may be associated with resistance against TB infection, but the studies do not evaluate the risk of developing active TB. Vitamin D deficiency has been reported to be common in patients with active TB (Gibney *et al.*, 2008; Nnoaham and Clarke, 2008) but a causal relation between vitamin D levels and TB remains to be established.

Interestingly, cod liver oil, which contains vitamin D, was used for treatment of TB in the pre-antibiotic era, as described already in a study from 1848, recently commented on by Green (2011). In a recent study it was also found that vitamin D supplementation to patients treated for pulmonary TB enhanced resolution of lymphopaenia, monocytosis, hypercytokinaemia, and hyperchemokinaemia. Supplementation also suppressed antigen-stimulated Th1 cytokine responses, but attenuated treatment induced suppression of antigen-stimulated IL-4, CCL5 and IFN- α secretion (Coussens *et al.*, 2012).

Taken together, these different observations and theoretical arguments make it reasonable to hypothesize that vitamin D substitution may have a beneficial effect on disease course in tuberculosis.

There is no standardised protocol for vitamin D supplementation in patients with active or latent TB. Worldwide, there are a large number of different supplements

available, and the treatment regimens vary between countries. In the Swedish guidelines for TB treatment, it is suggested that 75–125 µg ergocalciferol/day is given in vitamin D deficiency. Vitamin D oil or tablets with cholecalciferol are often used. Substitution with tablets containing calcium and cholecalciferol is an alternative in patients with coexisting hypocalcemia. There is no consensus on the optimal dose. In Sweden, 1600 IE/day has been suggested, but in many countries high loading doses are administered.

There is no clear consensus on reference values and the comparison of study results is complicated by the variability among the various assays available (Carter, 2009; Snellman *et al.*, 2010). The laboratory at Sahlgrenska University Hospital defines vitamin D deficiency as severe when 25OHD is < 25 nmol/l in serum, whereas 25-75 nmol/l is labeled as moderate deficiency, based on recommendations by The Endocrine society, USA (Holick *et al.*, 2011) and by Holick (2007) who define vitamin D deficiency as 25OHD <50 nmol/l and insufficiency as 52.5 - 72.5 nmol/l. The Institute of Medicine of the National academies (USA) states in a recent report that serum 25OHD levels of below 30 nmol/L (12 ng/mL) are related to risks for bone health (*e. g.* rickets and osteomalacia) and that there may also be a risk for some individuals at serum 25OHD levels between 30 and 50 nmol/L (20 ng/mL) (Ross *et al.*, 2011). The report did not find that higher levels were consistently associated with benefits for bone health (Ross *et al.*, 2011).

In patients with other conditions, normal values and treatment indications are not well defined, but studies indicate an association with increased all-cause mortality at levels below 30 nmol/l and (surprisingly) above 75-125 nmol/l (Ross *et al.*, 2011).

Patients undergoing treatment in Sweden are mainly immigrants from high TB incidence countries. No published data exist on the exact prevalence of vitamin D deficiency among these immigrants. However, preliminary reports from tertiary referral centers indicate that a majority of these patients have low levels of vitamin D. Thus, in VGR it is now common to measure vitamin D levels prior to initiation of treatment against TB and to supplement with vitamin D when deemed necessary.

3b The work group's understanding of the potential value of the health technology

As stated under 3a, there are some theoretical arguments for a beneficial effect of vitamin D on TB. Epidemiological data from VGR in Sweden show that an unexpected proportion of immigrants with latent TB have developed active TB with unique TB strains even after many years in Sweden and despite the lack of other risk factors (unpublished data).

Our hypothesis is that these cases represent reactivations of latent TB strains and that reduced vitamin D levels may contribute to these late reactivations. However, there are no published RCTs that have verified or rejected this hypothesis. If there is a causal link between low vitamin D levels and activation of TB, supplementation with vitamin D might prevent activation of latent TB and might also increase the susceptibility of active TB to current tuberculostatic therapy.

3c The central question for the current HTA project in one sentence

Does vitamin D supplementation, as compared to no treatment or placebo, reduce mortality, slow progression of disease, reduce disease susceptibility or increase the quality of life in patients with active or latent TB infection?

3d PICO

P= Patients, I= Intervention, C= Comparison, O=Outcome

P1= Patients with active tuberculosis, with or without treatment.

P2= Patients with latent tuberculosis, with or without treatment.

I = Vitamin D supplementation, with or without calcium supplementation.

C = Placebo, no treatment.

O1= Mortality.

Progression of disease.

Health-related quality of life.

Adverse events.

O2= Mortality.

Susceptibility to disease/development of disease.

Health-related quality of life.

Adverse events.

3e Key words

Tuberculosis, Vitamin D, Vitamin D deficiency

Tuberkulos, D-vitamin, D-vitaminbrist

Review of the Level of Evidence

4 Search strategy, study selection and references – Appendix 3

During September 2011, two librarians (TS, UWA) performed searches in PubMed, the Cochrane Library, Embase and a number of HTA-databases. Reference lists of relevant articles were also scrutinized for additional references. A total of 445 articles were identified after removal of duplicates, of which the librarians excluded 400 abstracts. The librarians excluded another 18 articles after being read in full text. Twenty-eight articles were sent to the work group for assessment. The literature search was updated in September 2012 and 104 references were found. Another three articles were sent to the project group, but none of these was added to the project. A total of thirteen articles were included in the report. Four articles were controlled studies and have been critically appraised. The appraisal of articles was based on checklists from SBU regarding RCTs (SBU, 2011).

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 3. The librarians (TS, UWA) conducted the literature searches and exclusion of abstracts, in consultation with the HTA-centrum and the work group.

5a Brief description of present knowledge of the health technology

Active tuberculosis

The literature search identified four RCTs and nine case series that fulfilled the inclusion criteria. The RCTs are listed in Appendix 1 and all included studies are listed in Appendix 3.

Mortality

Data on mortality in patients with active TB receiving supplemental vitamin D or placebo were obtained in two RCTs, Appendix 1:1. Both were considered to be of moderate quality. No significant effects on mortality were seen when vitamin D was added to standard treatment. Since normal vitamin D status was not an exclusion criterion in either study, we also separately evaluated the level of evidence in patients with confirmed vitamin D deficiency. No significant reduction in mortality of vitamin D supplementation was seen in this subgroup either. Low quality of evidence (GRADE ⊕⊕○○).

Progression of disease

Four RCT studies analysed effects of vitamin D supplementation on progression of disease, Appendix 1:2. Two were judged to be of high and two of low quality. The two RCTs of high quality found no significant advantages regarding progression of disease or clinical improvement with vitamin D treatment. One low-quality RCT reported a significantly reduced time to sputum smear conversion in the vitamin D group. The fourth study claimed to have found an effect on symptoms, but the presentation of the results was so weak that it is impossible to draw any conclusions from that study.

One of the high quality RCTs explored whether the effect of vitamin D supplementation might be modified by vitamin D receptor genotype, and found that patients with the *tt* genotype of the vitamin D receptor polymorphism had significantly shorter time to sputum culture conversion when receiving vitamin D.

In a recent study, Coussens *et al.* (2012) claim to have found that vitamin D supplementation accelerates sputum smear conversion ($p=0.04$) (Coussens *et al.* 2012). However, the patients belonged to the same study population included in the RCT by Martineau *et al.*, (2011), with the difference that Coussens *et al.* (2012) had added several exclusion criteria, *e. g.* receiving less than three doses of study medication and intake of oral steroids. Lack of clarity regarding the relation between the two patient populations and the high inherent risk for serious bias led to exclusion of this study.

No consistent effect of vitamin D supplementation on disease progression in patients with active TB was found. Very low quality of evidence (GRADE ⊕○○○).

Health-related quality of life

No studies fulfilling the PICO were identified.

Latent tuberculosis

No articles fulfilling the inclusion criteria for this patient group were identified.

Adverse events during Vitamin D supplementation

Few adverse effects were seen for vitamin D doses within the dose range used in Sweden today.

Some early studies used very high doses of vitamin D causing (expected) toxic symptoms (Appendix 5). Several case series of mainly cutaneous TB treated with high doses of vitamin D (50,000-180,000 IU/day) were published in the 1940s and 1950s (*e.g.* Ghosh, 1957; Grzybowski and Miedzinski, 1950; Ingram *et al.*, 1948; Lomholt, 1948; Marcussen, 1955; O'Donnell, 1947; Sonne and Lomholt, 1949; Wallis 1955), and toxic symptoms were common (16-33%). Symptoms were generally not considered dangerous and disappeared, even in serious cases, quickly after cessation of treatment.

In more recent reports where vitamin D was added to standard treatment of TB, the doses were lower ($\leq 4,000$ -10,000 IU/day) (*e.g.* Fuss *et al.*, 1988; Martineau *et al.*, 2011; Morcos *et al.*, 1998; Nursyam *et al.*, 2006; Wejse *et al.*, 2009). In these studies, toxicity was insignificant and only two cases of mild hypercalcemia were reported (Martineau *et al.*, 2011).

Questions have been raised about the risk of chronic overdosing of vitamin D in the absence of acute toxicity (Ross *et al.*, 2010). Further studies are needed, but there are some indications that levels above 75-125 nmol/l may have negative long-term effects.

5b Outcome tables – appendix 1

Appendix 1.

5c Excluded articles – appendix 2

Appendix 2.

5d **Ongoing research**

A search in the Clinical Trials database (www.clinicaltrials.gov), using the terms 'tuberculosis' and 'nutritional supplements', yielded 22 protocols. Six protocols aimed to study effects of vitamin D. One of the studies was withdrawn due to inadequate enrollment. Time to sputum conversion was the primary outcome in two of the five remaining studies. Other primary and secondary outcomes of the studies did not fall within the scope of the present HTA. Doses used in the studies were 800 IE/day (children 10-18 years), 50,000 IE single dose (infants), and 60,000 IE/week for two months followed by 60,000 IE/month for four months.

6 **Medical societies or health authorities that recommend the new health technology**

The guidelines on TB from the National Board of Health and Welfare (Socialstyrelsen, 2009) suggest an increased awareness of possible vitamin D deficiency in certain patient groups (dark skin or veil that prevents exposure to sun light). It is also stated that measurement of vitamin D may be of value, and supplementation is recommended if deficiency is detected. However, at present there are no clear national or local guidelines recommending routine test of vitamin D in all patients with active or latent TB.

- The National Board of Health and Welfare
- Medical societies
- Other health authority

Ethical aspects

7 **Ethical consequences**

There are few short term risks with medically indicated vitamin D supplementation, as long as overdosage is avoided. Very low vitamin D levels are quite common in certain immigrant populations, and therefore analysis of vitamin D levels is warranted irrespective of TB status. Serum levels of less than 30 nmol/l of 25-OH-vitamin D (25OHD) are associated with rachitis in children and osteomalacia in adults and there are also studies indicating increased overall mortality in persons with 25OHD < 30nmol/l. A very large proportion of the patients seen in our departments belong to this category. It therefore seems unethical not to test for and correct deficiencies with 25OHD levels below 30-50 nmol/l, even in the absence of solid evidence for a specific effect on TB. However, with vitamin D levels above this range, there is at least no scientific support for a positive effect on TB (active or latent). In the absence of data supporting patient benefit, introducing treatment on the basis of arbitrarily set laboratory values is ethically problematic.

Organisation

- 8a When the new health technology can be put into practice**
For patients who are seen in the clinics in VGR, the new health technology can be put to practice immediately. In order to reach individuals at risk for vitamin D deficiency that do not participate in the health examination for recently arrived immigrants a new organisation is needed. It would probably require at least a year to build up such an organisation, and still many individuals would not be reached.
- 8b Use of the technology in other hospitals in Region Västra Götaland of Sweden**
In VGR there is at present no standardised protocol including test and supplementation with vitamin D for TB patients. However, an increased awareness of vitamin D deficiency in certain patient groups has revealed a growing number of individuals considered to have severe vitamin D deficiency. As a consequence, there are an increasing number of patients receiving daily supplementation with vitamin D.
- 8c Consequences of the new health technology for personnel, according to the work group**
Since vitamin D sampling in most cases could be a part of the standard blood screen, there will be a marginally increased workload for nurses. With correct dosage, the risk for hypercalcemia is small, but nevertheless control of serum calcium is currently recommended and vitamin D levels may also need to be followed. Doctors will need to report results to patients/parents, prescribe vitamin D, modify dosage and motivate the patients/parents.
- 8d Consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland of Sweden?**
The number of blood samples assayed for vitamin D is expected to increase, and correspondingly increase the workload of the laboratory personnel.

Economy

9a Present costs of currently used technologies

When the HTA project started, vitamin D levels were routinely measured only at the Paediatric Department. Since then it has also become routine to measure vitamin D levels at the Department of Infectious Diseases. The cost of a 25OHD analysis is 250 SEK.

Vitamin D is available without prescription in oil or tablet form. The cost for the patient is about 50 SEK for 25 ml of vitamin D in oil (80IE/drop). The suggested dose of 1600 IE/day, generates a low cost for the patient (about 1 SEK/day).

There are also vitamin D drops with higher concentration (20,000 IE/ml) available on prescription only at a cost of 795 SEK for 10 ml, generating a daily cost of approximately 6 SEK for the patient. The vast majority of patients can take the cheaper formula.

In the departments of Infectious Diseases, Paediatrics, and Respiratory Medicine and Allergology, at Sahlgrenska University Hospital, the indications for testing and treatment would be active TB (A15-18) and latent TB (Z22.8) including both inpatients and outpatients, and also suspected deficiency in certain risk groups. In 2012 there were 110 reported cases of active TB in VGR. In the same year there were 40-50 patients with latent TB at the Paediatric Department. The figures are less certain for other departments, but approximately 70-100 patients per year with latent TB are referred to the Infectious Diseases Department at the Sahlgrenska University Hospital. Continued monitoring of vitamin D levels and substitution of deficiencies, after the completion of controls and/or treatment of TB at our respective departments, would require involvement of other care providers, most likely from the primary health care system.

9b Expected costs of the new health technology There will be no initial extra costs at the Departments of Infectious Diseases and Paediatrics at the Östra Hospital, since vitamin D levels are already routinely checked in these patients. Supplementation may increase the need for check of serum calcium levels. The cost for a 25OHD analysis is 250 SEK.

9c Total change of cost

The exact number of patients with latent TB is unknown. Therefore, we can only estimate the total change of costs. The sum paid for 100 patients is 25,000 SEK. Since testing will be done simultaneously with other blood tests, the cost for extra time for nurses is low. However, the technology may require life-long supplementation and blood sampling of vitamin D levels.

9d Possibility to adopt and use the new technology within the present budget (clinic budget/hospital budget)

Yes.

9e Available analyses of health economy, cost advantages or disadvantages

No studies analysing possible effects on health economics were identified.

Unanswered Questions

10a **Important gaps in scientific knowledge**

The patients fall into two major categories, those with very low (< 30 nmol/l) and those with low or normal vitamin D value. The first category should probably be treated irrespective of TB status (topic beyond present HTA report). Performing a randomised placebo controlled trial in this patient group raises ethical concerns. For the second category, a patient benefit of treatment is unproved, and here it should be possible to perform RCTs, particularly in the group with latent TB where there is no information at all. In addition, reference levels for vitamin D laboratory tests need to be established and seasonal variations accounted for.

10b **Interest in the own clinic/research group/organization to start studies/trials within the research field at issue**

Our work group is interested in starting studies/trials within the research field at issue.

Studies of vitamin D administration in patients with active TB have been performed and not shown a significant effect on mortality or progression of disease. There are to date, however, no RCTs on the effect of vitamin D supplementation in individuals with latent TB, but several studies that indicate that low vitamin D levels are associated with active TB. As TB is a serious illness, which requires at least six months of treatment, and vitamin D is cheap and non-toxic, it would be of great value if the development of active disease could be prevented by vitamin D supplementation. We are interested in designing a prospective RCT on the development of active TB in individuals who have received vitamin D as compared to persons who have received placebo. There is also a need to study vitamin D levels in different populations in Sweden more thoroughly to find out if all members of certain risk groups should be screened in order to prevent skeletal disorders, even in the absence of latent TB.

Statement from the HTA-centrum of Region Västra Götaland, Sweden

Vitamin D supplementation in patients with active or latent tuberculosis

Question at issue

Does vitamin D supplementation, as compared to no treatment or placebo, reduce mortality, slow progression of disease, reduce disease susceptibility or increase the quality of life in patients with active or latent tuberculosis (TB) infection?

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P2 = Patients with latent TB, with or without treatment.

I = Vitamin D supplementation, with or without calcium supplementation.

C = Placebo, no treatment.

O1 = Mortality.

Progression of disease.

Health-related quality of life.

Adverse events.

O2 = Mortality.

Susceptibility to disease/development of disease.

Health-related quality of life.

Adverse events.

Summary of the health technology assessment

Method and patient group

Patient value of vitamin D supplementation in patients with active or latent TB.

Level of evidence

PICO 1: Patients with Active TB

Four randomized controlled trials (RCTs) and nine case series fulfilled the inclusion criteria. No significant effect of vitamin D supplementation was seen on mortality in patients with active TB in the two studies which had this as an outcome (low quality of evidence, GRADE ⊕⊕○○).

No significant advantages regarding progression of disease in patients with active TB were found in the two RCTs of high quality. One low-quality RCT reported a significantly reduced time to sputum smear conversion in the vitamin D group. The fourth study claimed to have found an effect on symptoms, but the presentation of the results was so weak that it was impossible to draw any conclusions from that study (very low quality of evidence, GRADE ⊕○○○).

There were no studies with the outcome health-related quality of life on the effects of vitamin D supplementation in patients with active TB.

There were very few adverse events.

PICO 2: Patients with latent TB

No articles based on this patient group were identified.

Complications and side effects

With current substitution dosage (1600 IE/day), side effects were minimal or absent.

Ethical aspects

There are few risks with medically indicated vitamin D supplementation, as long as overdosage is avoided. Refraining from treatment due to lack of solid scientific evidence for a beneficial effect generates some ethical problems. Irrespective of TB status, serum levels of less than 30 nmol/l of 25-OH-vitamin D (25OHD) are associated with rachitis in children and osteomalacia in adults and there are also studies indicating increased overall mortality in persons with 25OHD < 30nmol/l. In certain risk groups, it therefore seems unethical not to test for and correct deficiencies with 25OHD levels below 30-50 nmol/l, even in the absence of solid evidence for a specific effect on TB.

Economical aspects

Testing for vitamin D deficiency is relatively inexpensive, but may involve many individuals leading to considerable costs, especially in the primary health care sector.

Concluding remarks

Vitamin D supplementation has no significant effect on mortality (low quality of evidence, GRADE ⊕⊕○○), or disease progression in patients with active TB (very low quality of evidence, GRADE ⊕○○○). No articles were identified studying the effect of vitamin D supplementation on quality of life in patients with active TB. Neither was any studies identified with these outcomes on patients with latent TB. In patients with very low vitamin D levels (25OHD levels below 30-50 nmol/l), treatment is probably indicated irrespective of TB status but this aspect was not analysed in the current HTA report.

On behalf of the HTA-centrum, Region Västra Götaland, Sweden

Göteborg, Sweden, 2012-03-28

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

The HTA was accomplished during the period of 2011-09-14—2012-11-26
Last search updated was in September 2012.

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Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

D-vitamin supplementering hos patienter med aktiv eller latent tuberkulos

Frågeställning

Leder D-vitamin tillskott till minskad dödlighet, långsammare sjukdomsprogression, lägre mottaglighet för sjukdomen, eller till förbättrad livskvalitet, hos patienter med aktiv eller latent tuberkulos (TB), i jämförelse med ingen behandling eller placebo?

PICO: (Patient, Intervention, Comparison, Outcome)

P1 = Patienter med aktiv TB, med eller utan behandling.

P2 = Patienter med latent TB, med eller utan behandling.

I = D-vitamin tillskott (med eller utan kalcium tillsats).

C = Placebo, ingen behandling.

O1 = Mortalitet.

Sjukdomsprogression.

Hälsorelaterad livskvalitet.

Sidoeffekter.

O2 = Mortalitet.

Mottaglighet i sjukdomen/utveckling av sjukdomen.

Hälsorelaterad livskvalitet.

Sidoeffekter.

Resultatet av HTA-processen:

Metod och målgrupp

D-vitamin bidrar till immunförsvaret och låga D-vitaminnivåer påvisas ofta vid hälsokontroller av invandrare från tropiska länder. Det finns en klinisk erfarenhet av att latent TB i denna population ibland aktiveras efter ankomsten till Sverige. Normalgränserna för D-vitaminnivåer är ofullständigt kända. Målet med HTA-analysen är att utreda dels om man med D-vitamin tillskott kan förbättra prognosen vid aktiv tuberkulos, och dels om man kan minska risken för aktivering av latent tuberkulos.

Evidensläge för studerad patientnytta

Fyra randomiserade kontrollerade studier (RCT) och nio fallserier uppfyllde inklusionskriterierna.

PICO 1: Patienter med aktiv TB

Ingen säkerställd effekt av D-vitamin tillskott kunde påvisas avseende mortalitet, i de två RCT som redovisade detta utfall, hos patienter med aktiv TB (begränsat vetenskapligt underlag, GRADE ⊕⊕○○).

Inga säkerställda fördelar av D-vitamin tillskott avseenden sjukdomsprogression kunde påvisas hos patienter med aktiv TB i de två RCT som var av hög kvalitet. En RCT av låg kvalitet rapporterade statistiskt säkerställd positiv effekt avseende tid till sputumkonvertering hos D-vitamin gruppen. Den fjärde RCTn som var av låg kvalitet redovisade effekt i form av symtom lindring, men resultatredovisningen var så bristfällig att inga slutsatser kunde dras från studien (otillräckligt vetenskapligt underlag, GRADE ⊕○○○).

Det fanns inga studier med utfallsmåttet hälsorelaterad livskvalitet avseende D-vitamin tillskott hos patienter med aktiv TB.

PICO 2: Patienter med latent TB

Inga artiklar där denna patientgrupp hade studerats kunde identifieras.

Komplikationer och sidoeffekter

Med gällande doseringsrekommendationer av D-vitamin tillskott (1600 IE/dygn) var sidoeffekterna minimala eller saknades helt.

Etiska aspekter:

Det finns få risker vid medicinskt indicerad D-vitamin supplementering, så länge som överdosering undviks. Att avstå från behandling med D-vitamin tillskott på grund av avsaknad av välunderbyggt vetenskapligt underlag skapar vissa etiska problem. Oavsett TB status är serumnivåer av 25-OH-vitamin D (25OHD) under 30 nmol/l förknippade med rakit hos barn och osteomalaci hos vuxna. Det finns även studier som indikerar ökad total mortalitet hos individer med 25OHD < 30 nmol/l. Avseende vissa riskgrupper kan det därför anses oetiskt att avstå från provtagning och från att supplementera med D-vitamin vid nivåer under 30-50 nmol/l 25OHD, trots avsaknad av välunderbyggt vetenskapligt underlag avseende specifika effekter på TB.

Ekonomiska aspekter

Provtagning avseende D-vitaminbrist är relativt billigt, men kan komma att omfatta många individer och därigenom bidra till betydande kostnader, särskilt i primärvården.

Sammanfattning och slutsats

D-vitamin supplementering har ingen säkerställd effekt på vare sig mortalitet (begränsat vetenskapligt underlag, GRADE ⊕⊕○○) eller sjukdomsprogression hos patienter med aktiv TB (otillräckligt vetenskapligt underlag, GRADE ⊕○○○). Inga artiklar som studerat effekter på livskvalitet för denna patientgrupp kunde identifieras. Underlag saknas också för att bedöma värdet av D-vitamin tillskott hos patienter med latent TB. Hos patienter med väldigt låga D-vitaminivåer (25OHD under 30-50 nmol/l), är behandling troligen indicerad oavsett TB status, men den aspekten av D-vitamin supplementering har inte analyserats i föreliggande HTA-rapport.

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerade teknologin.

Projektet har pågått under perioden 2011-09-14—2012-11-26

Sista uppdatering av artikelsökning 2012-09.

För HTA-kvalitetssäkringsgruppen 2012-03-28

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Appendix 1:1

Outcome variable: Effect of vitamin D supplementation on mortality in patients with active tuberculosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Vitamin D ₃	Control Placebo		
Martineau <i>et al.</i> , 2011	UK	RCT	146	11+9	n=62 One died during the study.	n=64 One died during the study.	Four doses of 2.5 mg vitamin D ₃ , or placebo, within 7 days, and at day 14, 28, and 42. Neither death was attributed to the study preparation.	Moderate
Weise <i>et al.</i> , 2009	Guinea-Bissau ¹	RCT	367	21*+12*	n=136 30 died during the study	n=145 23 died during the study p=0.45 (between groups)	*Mortality during the 12-month follow-up, here excluded from withdrawals and dropouts. 100,000 IU cholecalciferol, or placebo, given at inclusion, at 5 months, and at 8 months.	Moderate

¹The study was conducted in Guinea-Bissau by a Danish/Swedish research group.

Appendix 1:2

Outcome variable: Effect of vitamin D supplementation on disease progression in patients with active tuberculosis.

Author, year	Country	Study design	Number of patients n=	With drawals - drop-outs	Result		Comments	Quality (may vary according to outcome)
					Intervention Vitamin D ₃	Control		
Martineau <i>et al.</i> , 2011	UK	RCT	146	11+9	n=62, vitamin D ₃ Median time to sputum culture conversion: 36 days (95% CI 31.8-40.2 days)	n=64, placebo Median time to sputum culture conversion: 43.5 days (95% CI 36.5-50.5 days) p=0.41 (between groups)	Four doses of 2.5 mg vitamin D ₃ , or placebo, within 7 days, and at day 14, 28, and 42. (Enhanced response was seen for patients with tt genotype, p=0.02).	High
Morcos <i>et al.</i> , 1998	Egypt	RCT	24	0	n=12, vitamin D ₃ Increase in body weight: Mean 1.9 (0.6 SEM) p<0.005 (within group)	n=12, no vitamin D ₃ supplementation. Increase in body weight: Mean 2.6 (1.2 SEM) p<0.05 (within group)	1000 IU/day (children), or no supplementation, during eight weeks.	Low
Nursyam <i>et al.</i> , 2006	Indonesia	RCT	67	0	n=34, vitamin D ₃ 34/34 (100%) sputum culture conversion.	n=33, placebo 25/33 (77%) sputum culture conversion. P=0.002 (between groups)	0.25mg/day vit D3, or placebo supplementation, during six weeks.	Low
Weise <i>et al.</i> , 2009	Guinea-Bissau ¹	RCT	367	21*+12*	n=136, vitamin D ₃ Sputum smear conversion Changes in TB-score Median weight gain [†] : 5.9kg (11%)	n=145, placebo Sputum smear conversion rates were not different between the two groups among the 247 initially smear-positive patients. (data not shown). Changes in TB-score were not different between the groups (data not shown). Median weight gain [†] : 5.7 kg (12%) p=0.9 (between groups)	* Additional 30 individuals died in the intervention group, and 23 died in the placebo group during the 12-month follow-up. 100,000IU cholecalciferol, or placebo, given at inclusion, at 5 months, and at 8 months. [†] Measured at eight months	High

¹ Conducted in Guinea-Bissau by a Danish/Swedish research group
SEM=Standard Error of the Mean.

Appendix 2. Excluded articles

Study (author, publication year)	Reason for exclusion
Christopoulos <i>et al.</i> , 2009	No intervention (Vit D-treatment) given.
Coussens <i>et al.</i> , 2012	Duplicate publication with Martineau, 2011.
Epstein <i>et al.</i> , 1984	Outcome (Ca-metabolism) not concurrent with PICO.
Feeny <i>et al.</i> , 1947	No control group.
Ganmaa <i>et al.</i> , 2012	Outcome (TB skin test conversion) not concurrent with PICO.
Gertler, 1953	Outcome (blood pressure) not concurrent with PICO.
Gutierrez and Fernandez, 1950	No control group.
Gwinup <i>et al.</i> , 1981	Outcome (serum Ca concentration) not concurrent with PICO.
Holtz and Frohberg, 1957	Animal studies.
Horacek, 1948	No control group, insufficient data.
Martineau <i>et al.</i> , 2009	Outcome (Vit D-metabolism) not concurrent with PICO.
Narang <i>et al.</i> , 1984	Outcome (Serum Ca and K) not concurrent with PICO.
Nielsen <i>et al.</i> , 2010	No intervention (Vit D-treatment) given.
Pogorzelski and Miedzinski, 1954	No control group.
Roth <i>et al.</i> , 2004	No intervention (Vit D-treatment) given.

Appendix 2. Excluded articles

Study (author, publication year)	Reason for exclusion
Ruiter and Groen, 1949	No control group.
Schreus and Gahlen, 1955	Review.
Sinclair <i>et al.</i> , 2011	Review.

Appendix 3, Search strategy, study selection and references

Question(s) at issue:

Does vitamin D supplementation, as compared to no treatment or placebo, reduce mortality, slow progression of disease, reduce disease susceptibility or increase the quality of life in patients with active or latent TB infection?

PICO:

P1 = Patients with active tuberculosis, with or without treatment.

P2 = Patients with latent tuberculosis, with or without treatment.

I = Vitamin D (with or without calcium supplementation).

C = Placebo, no treatment.

O1 = Mortality.

Progression of disease.

Health-related quality of life.

Adverse effects.

O2 = Mortality.

Susceptibility of disease/development of disease.

Health-related quality of life.

Adverse effects.

Eligibility criteria

Study design:

Studies with control group

Case series with ≥ 10 patients

No case reports or review articles

Language:

English, German, Swedish, Norwegian, Danish

Publication date: No limitation

Search strategies

Database: PubMed

Date: 2011-09-28

No of results: 323

Search	Most Recent Queries	Result
#11	Search #8 NOT #9 Limits: English, German, Danish, Norwegian, Swedish	323
#10	Search #8 NOT #9	510
#9	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1123781
#8	Search #7 AND #2	549
#7	Search #6 OR #5	48010
#6	Search vitamin d[tiab] OR ergocalciferol[tiab] OR ergocalciferols[tiab] OR cholecalciferol[tiab] OR cholecalciferols[tiab]	30354
#5	Search "Vitamin D"[Mesh]	36371
#2	Search tuberculosis[Mesh] OR tuberculosis[tiab]	181957

Database: Embase (OVID SP)

Date: 2011-09-28

No of results: 262

#	Searches	Results
1	exp tuberculosis/	160349
2	tuberculosis.ti,ab.	129339
3	1 or 2	187807
4	exp vitamin D/	67512
5	exp ergocalciferol/ or ergocalciferol derivative/	5492
6	exp coledalciferol/ or exp coledalciferol derivative/	36248
7	(vitamin d or ergocalciferol or ergocalciferols or cholecalciferol or cholecalciferols or coledalciferol or coledalciferols).ti,ab.	34410
8	4 or 5 or 6 or 7	74482
9	3 and 8	854
10	limit 9 to (human and embase and (danish or english or german or norwegian or swedish) and article)	262

Database: The Cochrane Library
Date: 2011-09-28
No of results: 15
Cochrane reviews 1
Clinical trials 14

ID	Search	Hits
#1	(tuberculosis):ti,ab,kw	
#2	(vitamin D OR ergocalciferol OR ergocalciferols OR cholecalciferol OR cholecalciferols OR coledalciferol OR coledalciferols):ti,ab,kw	
#3	(#1 AND #2)	15

Search Updated: 2012-09-12

Database: Pubmed, Embase (OVID SP) and The Cochrane Library
No of results: 104

Database: CRD
Date: 2011-09-28
No of results: 5
NHS 2
DARE 3

ID	Search	Hits
#1	tuberculosis	
#2	Vitamin D OR ergocalciferol OR ergocalciferols OR cholecalciferol OR cholecalciferols OR coledalciferol OR coledalciferols	
#3	#1 AND #2	5

Search Updated: 2012-09-12

Nothing relevant in CRD and other HTA-databases was found

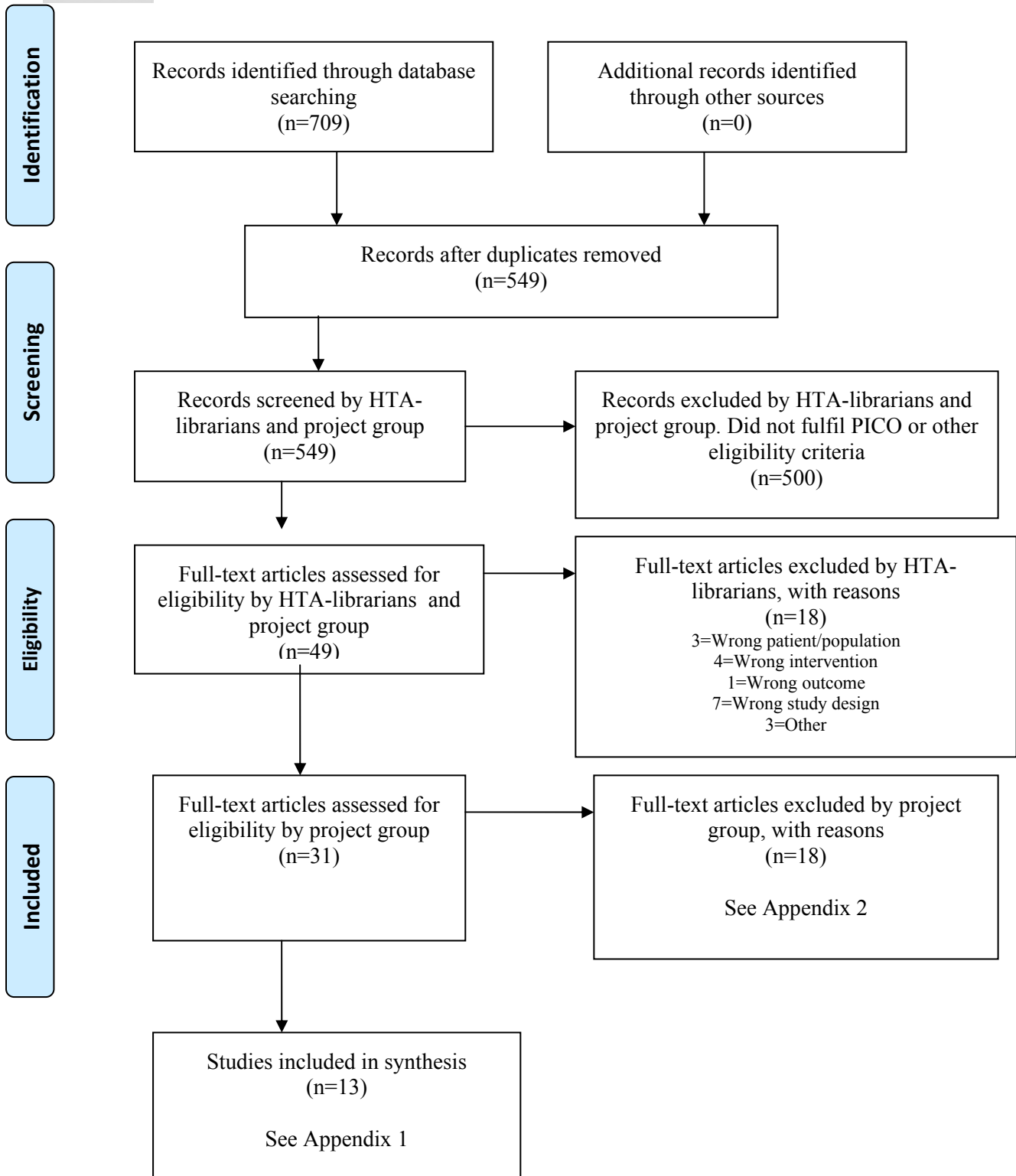
The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2011-10-26

Nothing relevant to the question at issue was found

Reference lists

No results

Selection process – flow diagram



Reference lists

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Appendix 4. Summary of Findings: Vitamin D supplementation in patients with active tuberculosis

Outcome variable	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Level of evidence GRADE
Number of studies										

Effect of Vit D on mortality in active TB										
2	RCT	Some limitations (0?)	No important inconsistency	Some uncertainty (0?)	Imprecision (-1)	Unlikely	Not relevant	Not statistically significantly	No significant difference	Low ⊕⊕○○
Effect of Vit D on disease progression in active TB										
4	RCT	Serious limitations (-1)	Some inconsistency (0?)	Some uncertainty (0?)	Imprecision (-1)	Unlikely	Not relevant	NA	No significant difference	Very low ⊕○○○

NA=Not analyzed. Four out of the six RCTs had sputum conversion as outcome, but the outcome was measured differently (App. 1-2).

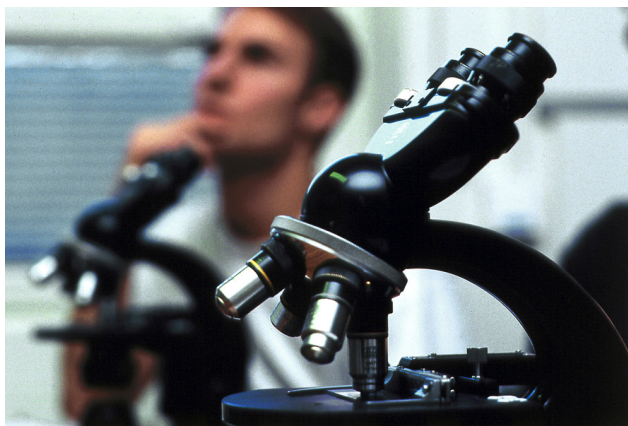
Appendix 5 Table Adverse events

First author / year	Abdominal pain	Anorexia	Blood pressure elevation	Conjunctivitis	Constipation	Diarrhea	Dizziness	Excessive thirst	Fever	Headache	Hypercalcemia	Nausea	Polyuria	Renal insufficiency	Serious adverse events	TB skin eruptions	Vomiting
High risk of toxicity																	
Ghosh 1952											-						
Grzybowski 1950		+				+	+	+			+	+	+				+
Ingram 1948	+	+			+					+	+	+	+			+	+
Lomholt 1947		+		+		+	+	+		+	+	+	+				+
Marcussen 1955			+						+		+						
O'Donnell 1947	+	+										+					+
Sonne 1949			+											+			
Wallis 1955																	
Low risk of toxicity																	
Fuss 1988											-						
Martineau 2011											+				+		
Morcos 1998											-						
Nursyam 2006											-						
Wejse 2009											-				-		

TB=Tuberculosis.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE ⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕○)
Low quality of evidence	= (GRADE ⊕⊕○○)
Very low quality of evidence	= (GRADE ⊕○○○)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

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Head of HTA-centrum

