Vitamin D and Cardiovascular Disease: are we at a tipping point?

Robert Scragg

School of Population Health, University of Auckland, Auckland, New Zealand

Abstract. Cardiovascular disease mortality is associated with temporally and geographically with low UV radiation, being increased in winter and in populations living at high latitudes, and decreased in populations living at high altitudes. UVB radiation is the primary source of vitamin D in humans, and several recent cohort studies have shown the low vitamin D levels at baseline predict increased risk of cardiovascular disease. However, randomised controlled trials of vitamin D supplementation are urgently required to provide certainty as to whether vitamin D protects against cardiovascular disease.

Background

Up until the 1970s, it was generally held by researchers active in the area that vitamin D was a cause of cardiovascular disease. This view point arose from animal studies showing that pharmacological doses of vitamin D (up to 5-10,000 IU per kg) resulted in arteriosclerosis. This was challenged in the 1970s by small case control studies, using the newly developed methods to measure 25-hydroxyvitamin D (25(OH)D), the main marker of vitamin D status. Contrary to expectations, these studies, including a case control study nested within a cohort from Tromsø, Norway (Vik, et al., 1979), found that myocardial infarction cases had similar or lower 25(OH)D levels than controls (Table 1).

A review of the descriptive epidemiology of cardiovascular disease, which has increased mortality in winter and at high latitudes, along with decreased mortality at high altitudes, lead to the idea by the author that UV radiation, by increasing vitamin D levels, may protect against cardiovascular disease (Scragg, 1981). This hypothesis was tested in a case control study carried out in Auckland in the 1980s which observed a significant inverse association between plasma levels of 25(OH)D and risk of myocardial infarction (Scragg, et al., 1990).

However, aside from a couple of small case control studies, no major epidemiological studies on vitamin D and cardiovascular disease were published until 2008. Since then, several cohort studies from community-based samples have been published, all showing inverse associations between baseline 25(OH)D levels and subsequent risk of cardiovascular disease. These cohort studies, which provide the best quality evidence on causation, aside from intervention studies, are reviewed below.

Cohort studies

The first published cohort study came from the offspring of the original participants in the well-known Framingham study which in the 1950-60s identified the major risk factors for cardiovascular disease. The recent Framingham Study Offspring Cohort followed 1,739 men and women (mean age 59 years) (Wang, et al., 2008).

Vik (1979), Tromso, Norway.
- Nested case control study. Data from 23 cases and 46 matched controls free of disease at baseline.
- 25(OH)D (Mean ±SD) in cases (59.0 ±24.1 nmol/L) was similar to controls (63.4 ±27.2); but lower in cases after correcting for blood level of vitamin D binding protein (p=0.024).

Wang (2008), Framingham, USA.
- Outcome: cardiovascular disease (fatal & non-fatal)
- Adjusted hazard ratio (95% CI) by category of 25(OH)D:
  - ≥15 ng/mL = 1.00
  - 10 to <15 ng/mL = 1.53 (1.00, 2.36)
  - <10 ng/mL = 1.80 (1.05, 3.08)

  p-value for linear trend = 0.01

Giovannucci (2008), male health professionals, USA.
- Outcome: coronary heart disease (fatal & non-fatal)
- Adjusted odds ratio (95% CI) by category of 25(OH)D:
  - ≥30 ng/mL = 1.00
  - 22.6-29.9 ng/mL = 1.60 (1.10, 2.32)
  - 15.1-22.5 ng/mL = 1.43 (0.96, 2.13)
  - ≤15.0 ng/mL = 2.09 (1.24, 3.54).

  p-value for linear trend = 0.02

Ginde (2009), US representative sample (NHANES).
- Outcome: cardiovascular disease (fatal only)
- Adjusted hazard ratio (95% CI) by category of 25(OH)D:
  - <25.0 nmol/L = 1.83 (1.14, 2.94)
  - 25.0-49.9 nmol/L = 1.47 (1.09, 1.97)
  - 50.0-74.9 nmol/L = 1.21 (0.92, 1.59)
  - 75.0-99.9 nmol/L = 1.15 (0.86, 1.53)
  - ≥100.0 nmol/L = 1.00

Kilkkinen (2009), Mini-Finland Health Survey, Finland.
- Outcome: cardiovascular disease (fatal only)
- Adjusted hazard ratio (95% CI) by quintile of 25(OH)D:
  - Quintile 1 (low) = 1.00
  - Quintile 2 = 1.04 (0.86, 1.26)
  - Quintile 3= 0.81 (0.66, 1.00)
  - Quintile 4 = 0.86 (0.70, 1.06)
  - Quintile 5 (high) = 0.76 (0.61, 0.95)

  p-value for linear trend = 0.005

Pilz (2009), Hoorn Study, Holland
- Outcome: cardiovascular disease (fatal only)
- Adjusted hazard ratio (95% CI) by quartile of 25(OH)D:
  - Upper 3 quartiles = 1.00
  - First quartile (low) = 5.02 (1.88, 13.42)

Semba (2010), InCHIANTI Study, Italy.
- Outcome: cardiovascular disease (fatal only)
- Adjusted hazard ratio (95% CI) by quartile of 25(OH)D:
  - <10.5 ng/mL = 2.57 (1.12, 5.91)
  - 10.5-16.0 ng/mL = 1.76 (0.80, 3.89)
  - 16.1-25.6 ng/mL = 2.28 (1.09, 4.79)
  - >25.6 ng/mL = 1.00

Table 1. Summary of community-based cohort studies of blood levels of 25-hydroxyvitamin D and cardiovascular disease.

Table 1 shows increased hazard ratios of dying from cardiovascular disease during the 5-year follow-up period in the Framingham Offspring study, compared to the reference group (baseline 25(OH)D ≥15 ng/ml), adjusted for demographic variables, blood pressure, blood lipids, cigarette smoking and body mass index.

The second publication was a nested case control study, from within a cohort study of 18,225 US male health professionals aged 40-75 years followed for 10 years (Giovannucci, et al., 2008). This study found a significant inverse association (p=0.02) between baseline plasma 25(OH)D and risk of coronary heart disease, adjusted for demographic and cardiovascular variables including month of blood collection, history of hypertension and diabetes, blood lipids, smoking status, alcohol intake, physical activity and body mass index (Table 1).

The third study was from the Third National Health and Nutrition Examination Survey (NHANES), a random sample of the US civilian population, which was originally surveyed in 1988-94 and followed-up for mortality until 2000 (Ginde, et al., 2009). A significant inverse association was found between baseline 25(OH)D level and risk of cardiovascular death during follow-up in participants aged ≥65 years at baseline, adjusted for demographic and cardiovascular variables including season of blood collection, BMI, physical activity, smoking, blood pressure and blood lipids (Table 1).

The fourth study was the Mini-Finland Health Survey, which interviewed in 1978-1980 6,219 Finns selected randomly from a population register, and followed them up to 2006 (Kilkkinen, et al., 2009). Risk of cardiovascular death decreased significantly with increasing baseline 25(OH)D (p=0.005), adjusted for demographic and a wide range of cardiovascular variables including season, BMI, smoking, leisure-time physical activity and alcohol intake (Table 1).

The fifth cohort study to publish results was the Hoorn Study from Holland, which interviewed 614 participants, recruited from a municipal register, in 2000-2001 (mean age 70 years) and followed them until July 2007 (Pilz, et al., 2009). Participants in the lowest quartile of baseline 25(OH)D had a 5-fold increased risk of dying from cardiovascular disease, compared to those in the other three quartiles, adjusting for demographic variables and a wide range of cardiovascular variables including smoking, physical activity, waist-to-hip ratio, blood pressure, HDL-cholesterol, and kidney function (Table 1).

The sixth study published to-date comes from the InCHIANTI study, Italy, which examined 1006 people aged ≥65 years recruited from a population register in 1998-1999 and followed for 6.5 years (Semba, et al.). This study found that people with baseline 25(OH)D levels in the lowest quartile had an approximate 2.5 fold increased risk of dying from cardiovascular disease compared with those in the highest quartile (Table 1).

Conclusion

All cohort studies of community selected samples have reported significant inverse associations between baseline blood vitamin D levels and risk of developing or dying from cardiovascular disease during the follow-up period (Table 1). Collectively, these are very compelling results which suggest that vitamin D may reduce the risk of developing cardiovascular disease. However, over the last 10-15 years there have been several examples of exposure-disease associations observed in cohort studies which have not been confirmed by clinical trials. These include hormone replacement therapy and cardiovascular disease, beta-carotene and cancer, and vitamin E and cardiovascular disease.

We are indeed at a tipping point, with regard to vitamin D and cardiovascular disease. While cohort studies provide strong evidence to support a causal association between low vitamin D status and increased risk of cardiovascular disease, certainty about the association will only come from large randomised clinical trials designed to determine if vitamin D supplementation reduces the risk of cardiovascular disease. There is an urgent public health need to do such studies, as vitamin D is very cheap (a year's supply costs about $5), and could be given at low cost to large sections of the population if vitamin D is shown to be beneficial.

References

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