Vitamin D for the prevention of type 2 diabetes

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2015

document version
Publisher's PDF, also known as Version of record

Summary

This thesis contains an array of studies addressing the role of vitamin D in non-skeletal health, i.e. the metabolic syndrome, glucose tolerance, physical activity, testosterone, and also provides a search towards a possible prevention strategy for diabetes mellitus in the future. The rationale for the studies was the fact that diabetes mellitus type 2 has become a serious global health problem with the expectation that without effective prevention strategies, the burden will continue to increase globally. We focused primarily on the elderly and non-western immigrants in the Netherlands, because the prevalence of diabetes and the metabolic syndrome is high among these populations.

Recently, much attention is being given to the relation of vitamin D status to diabetes mellitus. Several epidemiological and clinical studies suggest an increased risk of type 2 diabetes mellitus (DM2) among persons with vitamin D deficiency. At present, a debate on the possible causal relation between vitamin D and diabetes is going on.

In **chapter 2** we assessed the association between vitamin D status and the metabolic syndrome in the elderly (> 65 year) in the Longitudinal Aging Study Amsterdam (LASA) study, an ongoing cohort study in a representative sample of Dutch older persons. A total of 1286 subjects participated in the study. The metabolic syndrome was observed in more than one third of the study participants, and the average serum 25(OH)D level was 53.3 ± 24.1 nmol/l. A serum 25(OH)D level below 50 nmol/l was associated with an increased risk of the metabolic syndrome, compared to serum 25(OH)D levels above 50 nmol/l, after adjustment for confounders. The adjusted odds ratio was 1.29 (95% CI 1.00-1.68).

In **chapter 3** the results of a randomized, placebo-controlled trial in non-western immigrants, with vitamin D deficiency and at high risk for diabetes (n=130) were reported. In this trial, the effect of vitamin D supplementation on insulin sensitivity was investigated. We hypothesized that vitamin D supplementation could have a positive effect on insulin resistance and β-cell function in people with vitamin D deficiency and at risk for diabetes. The subjects included in this trial had fasting glucose levels > 5.5 mmol/l or random glucose levels of 7.8-11.1 mmol/l and 25(OH)D < 50 nmol/l. Furthermore, the participants had a BMI > 27 kg/m2 and the mean serum 25(OH)D level at baseline was 23.4 mmol/l ± 10.7. Daily supplementation with 1200 IU cholecalciferol in combination with 500 mg calcium did not have an effect on glycaemia and insulin sensitivity parameters, measured with oral glucose tolerance testing after 4 months of intervention, compared to the control, who received placebo and 500 mg calcium. The lack of effect was not in line with our initial hypothesis. However, in a post-hoc analysis, when patients with diabetes at baseline were excluded, a significant increase in insulinogenic index was observed in participants who obtained a 25(OH)D concentration of ≥ 60 nmol/l after intervention. (P=0.040) (27 subjects in the intervention group, 54 subjects in the placebo group)

In **chapter 4** the influence of vitamin D supplementation on physical activity and per-

formance in the same randomized-placebo controlled clinical trial is described. The percentage of participants meeting the international physical activity guidelines in this trial was extremely low, less than 10 %. There was no effect of 1200 IU cholecalciferol on the different physical performance and activity scores. These scores included the physical performance score (calculated from the tandem test, the chair stand test and walking test), exercise capacity (six minutes walk test, 6-MWT)) and daily physical activity (questionnaire and accelerometer). In a post-hoc analysis restricted to participants reaching a serum 25(OH)D level of > 60 nmol/l after intervention, there was a non-significant effect (P=0.053) of 19 meters increase of the walking distance measured with 6-MWT in the intervention group. The clinical importance of this increase has not been validated in this specific population. In postoperative subjects, a clinical meaningful difference of 19 meter between groups has been reported earlier.(1)

In **chapter 5** the association between vitamin D status and testosterone levels in men is presented on the basis of data from three earlier vitamin D trials, including data of men from our randomized trial. In addition, the effect of vitamin D supplementation on testosterone levels is presented in this chapter. Study 1 consisted of 92 men with heart failure who received 2000 IU of vitamin D or placebo for 6 weeks. In study 2, 49 vitamin D deficient men received either 600 IU of vitamin D or placebo for 4 months. In study 3 (our randomized trial), 43 vitamin D deficient non-western immigrant men received 1200 IU of vitamin D or placebo for 16 weeks. There was an association between vitamin D status and serum testosterone at baseline in agreement with the existing literature, but vitamin D supplementation did not alter testosterone levels in the three different studies.

In **chapter 6** we investigated the association between the bone formation marker osteocalcin and the metabolic syndrome in the LASA cohort study. Our hypothesis was that low plasma osteocalcin levels are associated with a higher risk for the metabolic syndrome. Plasma osteocalcin was clearly, inversely associated with the metabolic syndrome with an adjusted odds ratio of 3.69 (95% CI 2.53-5.34) for the lowest osteocalcin quartile compared to the subjects in the highest osteocalcin quartile, which is in line with our hypothesis and is in accordance with recent literature.

In conclusion, we found a clear association between vitamin D status and the metabolic syndrome, but no clear effect of vitamin D supplementation on insulin sensitivity parameters, except a possible small effect on insulin secretion in subjects with the most explicit increase in 25-hydroxyvitamin D levels. Further research is needed to prove a possible causal relationship. Furthermore, we found an association between the bone formation marker osteocalcin and the metabolic syndrome, which is a base for new research strategies. Next to this, we explored the effects of vitamin D supplementation on physical activity and testosterone levels in male subjects, which revealed minor effects on 6-MWT and no effect on testosterone levels.