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Institutionen för molekylär medicin och kirurgi

Factors affecting the development of type 2 diabetes and cardiovascular disease, with special reference to vitamin D

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ABSTRACT

There is increasing evidence that vitamin D may influence several non-skeletal conditions, including cardiovascular disease (CVD), diabetes, cancer, autoimmune disorders and infectious diseases. Vitamin D is among the few vitamins that can be produced by the skin in response to ultraviolet B radiation. Vitamin D is also a prohormone that is converted to 25-hydroxyvitamin D (25(OH)D) in the liver and 1,25-dihydroxyvitamin D (a hormone) in the kidneys. In addition, vitamin D receptors are present in most tissues and cells in the body. Many tissues and cells, including, colon, prostate, pancreatic β-cells and macrophages, express the enzyme 1α-hydroxylase to locally produce 1,25-dihydroxyvitamin D, which has the potential to regulate a number of genes. The pleiotropic effect of vitamin D may favorably influence diabetes and cardiovascular health through multiple mechanisms, including downregulation of the renin-angiotensin system, enhancement of insulin secretion and insulin sensitivity, protection against angiogenesis and modulation of inflammatory processes.

Epidemiological evidence suggests that vitamin D may reduce the risk of developing type 2 diabetes (T2D) and CVD. However, so far, studies found mixed results and data have been inconclusive. We aimed to investigate: 1) Whether low serum 25(OH)D concentrations predict the development of prediabetes and T2D; 2) The relationships between serum 25(OH)D concentration and established or emerging cardiovascular risk factors and risk of myocardial infarction (MI); 3) Serum 25(OH)D in relation to baseline severity and rate of progression of carotid intima-media thickness (cIMT); and 4) Whether vitamin D is causally implicated in CVD using vitamin D-associated genetic variants, serum 25(OH)D concentration and progression of subclinical carotid atherosclerosis.

In **Paper I**, subjects aged 35-56 years, without known T2D, underwent a health examination, including measurements of weight, height and blood pressure (BP), an oral glucose tolerance test (OGTT) was performed, and questionnaires covering life-style factors were answered at baseline and at follow-up. Serum 25(OH)D and serum insulin growth factor peptides were measured at baseline. Participants having prediabetes or T2D at follow-up 8-10 years later were selected as cases, age- and sex-matched to controls with normal glucose tolerance at both baseline and follow-up, in total 980 women and 1398 men. We found that high serum 25(OH)D concentrations predict reduced T2D risk in subjects having prediabetes but not in subjects with normal glucose tolerance. In **Paper II**, a total of 387 survivors of a first MI before the age of 60 and 387 sex- and age-matched controls were examined. Fasting blood samples, drawn three months after MI in cases and at the same time in matched controls, were used for biochemical analyses. Low 25(OH)D levels were associated with a range of cardiovascular risk factors but were not related to MI. Both **Paper III and IV** are based on the IMPROVE study, which is a European, multicentre, longitudinal cohort study that enrolled individuals aged 54 to 80 years, who had at least three cardiovascular risk factors and no history of CVD, from 7 centers in Finland, Sweden, the Netherlands, France, and Italy. Participants underwent carotid ultrasound examinations at baseline, month 15 and month 30. Blood samples, clinical data and information about life-style factors were collected at baseline from a total of 3,711 subjects, upwards of 900 of whom had diabetes. The results reported in **Paper III** demonstrated that levels of 25(OH)D differed across Europe and were not consistently, independently related to measures of cIMT. In **Paper IV**, we found one genetic variant (rs3829251) in the *DHCR7* (7-dehydrocholesterol reductase) gene which influenced progression of cIMT in a manner dependent on T2D status but independent of 25(OH)D levels.

Key words: *Type 2 diabetes, prediabetes, Vitamin D, 25-hydroxyvitamin D, Cardiovascular disease, Carotid intima-media thickness, Subclinical atherosclerosis, Single nucleotide polymorphisms.*

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