The vitamin D-binding protein Gc

Measurement and clinical utility

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ABSTRACT

The PhD study was carried out in the Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus Sygehus, Norrebrogade.

The vitamin D-binding protein Gc is a multifunctional plasma protein that among other things plays a role for transport of vitamin D and for activation of macrophages and osteoclasts.

The aim of the study was to establish methods for Gc measurement, and examine the influence of Gc phenotype and Gc concentration on vitamin D status, bone tissue, and bone fracture risk, as well as estimation of urinary Gc loss in kidney diseases.

We have established four methods for characterization and measurement of Gc:

- Phenotyping by isoelectric focusing
- Genotyping by melting curve analysis (SNP analysis)
- Quantification in plasma by immunonephelometry
- Quantification in urine and other samples with low Gc concentration by a sensitive, automated ELISA

By isoelectric focusing, we identified the Gc phenotype of 595 Caucasian early postmenopausal women enrolled into the Danish Osteoporosis prevention Study (DOPS). Plasma levels of Gc, 25-hydroxy-vitamin D, and 1,25-Dihydroxy-vitamin D differed significantly between women with different Gc phenotype, being highest in Gc1-1, intermediate in Gc1-2, and lowest in Gc2-2. Sixty per cent of the women with the phenotype Gc2-2 had plasma 25-hydroxy-vitamin D below 50 nmol/L without any signs of vitamin D insufficiency. We suggest that the thresholds for vitamin D insufficiency differ between persons with various Gc phenotypes.

Of the 595 women, 179 (30%) had a history of one or more bone fractures before menopause. The fracture frequency varied significantly (p=0.017) according to Gc phenotype, being highest in women with Gc1-1 (34%), intermediate in Gc1-2 (27%), and lowest in Gc2-2 (14%). By using logistic regression analysis, we found the relative risk of premenopausal bone fracture to be 0.32 (0.13-0.80) for Gc2-2 compared to Gc1-1. We propose that the Gc phenotypes cause differences in osteoclast activity, a hypothesis supported by our finding of lower plasma levels of the macrophage marker soluble CD163 in women with Gc2-2.

Our results suggest that Gc genotyping could be used to identify individuals with increased bone fracture risk and thus in need of preventive treatment. This provided that our results are confirmed also in older women and in men.

By use of our sensitive ELISA method, we quantified Gc in the urine from 99 patients with various kidney diseases. The 24 h urinary loss of Gc ranged from 0.002 mg to 47 mg. A significant negative correlation between Gc/albumin ratio in second-void urine and creatinine clearance, indicates that when the kidney function deteriorates, the Gc/albumin ratio in urine increases. Longitudinal studies are now requested to test the utility of urinary Gc/albumin as a marker of kidney function.