USEFUL FOR
As a screening test for inactivating CYP24A1 mutations in patients with symptoms, signs, or biochemical findings of parathyroid hormone (PTH)-independent hypercalcemia or hypercalciuria.

CLINICAL INFORMATION
Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols. The 25HDN / 25-Hydroxyvitamin D2 and D3. Serum assay is the preferred initial test for assessing vitamin D status and most accurately reflects the body's vitamin D stores. In the presence of renal disease, DHVD / 1,25-Dihydroxyvitamin D, Serum testing might be needed to adequately assess vitamin D status. For patients with loss of function inactivating CYP24A1 mutations, this test (2425D / 25-Hydroxyvitamin D2 and D3:24,25-Dihydroxyvitamin D Ratio, Serum) may be helpful. Loss of function mutations in the CYP24A1 gene have been shown to lead to insufficient deactivation of bioactive vitamin D metabolites, resulting in a phenotype characterized by suppressed serum parathyroid hormone (PTH), increased serum 1,25-dihydroxyvitamin D (DHVD) concentrations, hypercalcemia, and hypercalciuria or nephrolithiasis.

Vitamin D compounds in the body are exogenously derived by dietary means; from plants as 25-hydroxyvitamin D2 (ergocalciferol or calciferol) or from animal products as 25-hydroxyvitamin D3 (cholecalciferol or calcidiol). Vitamin D may also be endogenously derived by conversion of 7-dihydrocholesterol to 25-hydroxyvitamin D3 in the skin upon ultraviolet exposure. 25-Hydroxyvitamin D (25HDN) is subsequently formed by hydroxylation (CYP2R1) in the liver. 25HDN is a prohormone that represents the main reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. Biological activity is expressed in the form of DHVD the active metabolite of 25HDN. 1-Alpha-hydroxylation (CYP27B1) occurs on demand, primarily in the kidneys, under the control of parathyroid hormone (PTH) before expressing biological activity. Like other steroid hormones, DHVD binds to a nuclear receptor, influencing gene transcription patterns in target organs.

25HDN may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by (CYP24A1) hydroxylation. This process regulated by parathyroid hormone (PTH) might increase DHVD synthesis at the expense of the alternative hydroxylation (CYP24A1) product 24,25D. Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents over production of DHVD and resultant vitamin D toxicity.

REFERENCE VALUES
Review reference values at: MayoMedicalLaboratories.com

ANALYTIC TIME
2 days

SPECIMEN REQUIRED
Type
Serum
Container/Tube
Preferred: Red top
Specimen Volume
3 mL
Collection Instructions
Spin down within 2 hours of draw.

04/2018

CONTENT AND VALUES SUBJECT TO CHANGE. SEE THE MAYO MEDICAL LABORATORIES TEST CATALOG FOR CURRENT INFORMATION.
DHVD stimulates calcium absorption in the intestine and its production is tightly regulated through concentrations of serum calcium, phosphorus, and PTH. DHVD promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition, or less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH mRNA expression in the PTH glands is downregulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism, DHVD regulates the expression of a multitude of genes in many other tissues including immune cells, muscle, vasculature, and reproductive organs.

DHVD levels are decreased in hypoparathyroidism and in chronic renal failure. DVHD levels may be high in primary hyperparathyroidism and in physiologic hyperparathyroidism secondary to low calcium or vitamin D intake. Some patients with granulomatous diseases (eg, sarcoidosis) and malignancies containing nonregulated 1-alpha hydroxylase in the lesion might have hypercalcemia that appears vitamin D mediated with normal or high serum phosphate (hyperphosphatemia) and hypercalcemia (both of which might be severe), in addition to low parathyroid hormone (PTH) and absent parathyroid hormone-related peptide (PTHRP). Differential diagnostic considerations include vitamin D intoxication and CYP24A1 deficiency.

**INTERPRETATION**

Results should be interpreted in the context of other biochemical findings including serum calcium, parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D (DHVD) concentrations. If 25-hydroxyvitamin D (25HDN) result is less than 20 ng/mL, the ratio of 25-OH-D to 24,25-dihydroxyvitamin D (24,25D) will be falsely elevated since there is no inactivation of 25-OH-D to 24,25D.


Ratios of 25HDN to 24,25D less than 25 may be interpreted as normal, though ratio of less than 25 may also be observed in heterozygous carriers of CYP24A1 mutations.

Ratios of 25HDN to 24,25D between the 25 and 80 range may be seen in patients with low vitamin D or heterozygous CYP24A1 mutations. Confirmation with molecular testing is recommended.

Confirmation with molecular testing is also recommended for ratios of 25HDN to 24,25D greater than 80, as this may indicate a probable biallelic CYP24A1 mutation or deletion.

**CLINICAL REFERENCE**