

Vitamin D Levels May Set Stage for Heart Disease

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Vitamin D deficiency may increase the risk of cardiovascular disease in adults, especially in people who also have hypertension, based on data from the Framingham Offspring Study.

More studies are needed to show whether correcting vitamin D deficiency could prevent or reduce the risk of cardiovascular disease, but the clinical impli-

cation of the finding is that correcting the deficiency, which is prevalent worldwide, could have a significant effect on public health, according to the study's authors.

Previous clinical studies have shown associations between lower levels of vitamin D and an increased risk of problems including prevalent cardiovascular disease, coronary artery calcification, and plasma renin activity (an indicator of high blood pressure). These associations may occur in part because vitamin D receptors are

found in a range of tissues including vascular smooth muscle tissue, the lining of the interior surface of blood vessels, and heart muscle tissue.

But more data are needed to show whether vitamin D deficiency is a result of cardiovascular disease or a contributing factor. To determine the relationship between vitamin D status and the incidence of cardiovascular events in a population with no history of cardiovascular disease, Dr. Thomas J. Wang of Harvard Medical

School, Boston, and his colleagues followed 1,739 participants in the Framingham Offspring Study for at least 5 years. The average age of the participants was 59 years, 55% were women, and all were white. The study consists of the children of participants in the original Framingham Heart Study that began in 1948.

In this study, a 25-hydroxyvitamin D (25-OH D) level lower than 15 ng/mL was used to define vitamin D deficiency. This value was chosen for consistency with other cross-sectional studies of the Framingham data and with hospital-based samples, although 25-OH D levels greater than 30 ng/mL are considered preferable for promoting bone metabolism, the researchers noted.

At the start of the study, 28% of the participants had 25-OH D levels lower than 15 ng/mL, and 9% had levels lower than 10 ng/mL (Circulation 2008 Jan. 29 [Epub doi:10.1161/circulationaha.107.706127]).

A total of 120 participants had a cardiovascular event after an average of 5.4 years of follow-up (approximately 8,069 person-years). Overall, those with 25-OH D levels lower than 15 ng/mL were significantly more likely to have had a cardiovascular event than were those whose 25-OH D levels were 15 ng/mL or higher. After adjusting for age and sex, the 5-year incidence rate was more than twice as high in those with 25-OH D levels lower than 15 ng/mL than in those with higher levels (4.4 vs. 8.9).

In particular, the highest rates of cardiovascular event risk were observed in subjects with hypertension as well as vitamin D deficiency. The 5-year rate of cardiovascular disease was more than twice as high in the subjects with hypertension and vitamin D deficiency, compared with the hypertensive subjects who were not vitamin D deficient (5.8 vs. 14.2).

Furthermore, the higher cardiovascular risk appeared to increase as vitamin D decreased in the hypertensive patients. When vitamin D levels were divided into three categories, the hazard ratios were 1.00, 1.93, and 2.51 for those with 25-OH D levels of 15 ng/mL or higher, 10-15 ng/mL, and lower than 10 ng/mL, respectively. But no similar progressions across categories of 25-OH D deficiency were noted among nonhypertensive subjects.

The cardiovascular events included 65 fatal or nonfatal coronary heart disease events, 28 fatal or nonfatal cerebrovascular events, 19 cases of heart failure, and 8 instances of claudication.

The study was limited because not all variables that affect vitamin D were measured. But using an objective measure of vitamin D (25-OH D) rather than relying on subjects' self-reports of vitamin D intake makes the findings stronger.

Although the findings suggest that treating vitamin D deficiency could reduce the risk of heart disease, the findings are not enough to advise a treatment plan, and more clinical and experimental research is needed. The study was supported in part by grants from the American Heart Association, the U.S. Department of Agriculture, and the National Institutes of Health. Dr. Wang, the lead author, had no financial conflicts to disclose. ■

ADVERSE REACTIONS

Clinical Trials Experience. The overall incidence of side effects reported in patients receiving sitagliptin and metformin was similar to that reported with patients receiving placebo and metformin.

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice-daily metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in $\geq 5\%$ of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

The overall incidence of adverse reactions of hypoglycemia in patients treated with sitagliptin and metformin was similar to patients treated with placebo and metformin (100 mg sitagliptin and metformin, 1.3%; placebo and metformin, 2.1%). Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The incidence of selected gastrointestinal adverse reactions in patients treated with sitagliptin and metformin was also similar to placebo and metformin: nausea (sitagliptin and metformin, 1.3%; placebo and metformin, 0.8%), vomiting (1.1%, 0.8%), abdominal pain (2.2%, 3.8%), and diarrhea (2.4%, 2.5%).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed with the combination of sitagliptin and metformin.

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in $\geq 5\%$ of patients and more commonly than in patients given placebo was nasopharyngitis.

The most common ($>5\%$) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Laboratory Tests

Sitagliptin. The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride. In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ supplementation [see Warnings and Precautions].

Postmarketing Experience. The following additional adverse reactions have been identified during postapproval use of sitagliptin, one of the components of JANUMET. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

DRUG INTERACTIONS

Cationic Drugs. Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Digoxin. There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. These increases are not considered likely to be clinically meaningful. Digoxin, as a cationic drug, has the potential to compete with metformin for common renal tubular transport systems, thus affecting the serum concentrations of either digoxin, metformin or both. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUMET is recommended.

Glyburide. In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide. A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine. A single-dose, metformin-nifedipine drug interaction study in normal healthy

volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

The Use of Metformin with Other Drugs. Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B.

JANUMET. There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. JANUMET should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to JANUMET while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUMET by calling the Pregnancy Registry at (800) 986-8999.

No animal studies have been conducted with the combined products in JANUMET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin. Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Metformin hydrochloride. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers. No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET is administered to a nursing woman.

Pediatric Use. Safety and effectiveness of JANUMET in pediatric patients under 18 years have not been established.

Geriatric Use. **JANUMET.** Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function [see Warnings and Precautions].

Sitagliptin. Of the total number of subjects (N=3884) in Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride. Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function [see Contraindications; Warnings and Precautions].



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