Noncommunicable diseases (NCDs), namely, cardiovascular diseases, diabetes, obesity, cancer, and chronic respiratory diseases, were identified by the World Health Organization as the leading cause of death, accounting for two thirds of all causes of deaths worldwide [1]. These diseases are projected to further increase in view of global urbanization, sedentary lifestyle, and increased life expectancy in populations across the globe. Abdominal obesity, hyperglycemia, dyslipidemia, and hypertension, core traits of the metabolic syndrome (MetS) phenotype, account in large part for the rising tide in these NCDs [2]. The prevalence of MetS has swiftly risen from 22% in 1988-1994 to 34.5% in 1999-2002 in the United States National Health and Nutrition Examination Survey [3]. Similar trends are noted worldwide in general and in the Middle East in particular, where obesity rates in some countries reach 40% to 70%, exceeding those in Western countries [4]. This region also registers the greatest relative increase in diabetes prevalence, with rates reaching 20% in Bahrain, Saudi Arabia, and the United Arab Emirates [4].

Vitamin D is naturally present in only few foods and is in large part endogenously produced when solar ultraviolet rays (290-315 nm) trigger vitamin D synthesis in the skin that is then mostly stored in fat [5]. It is thus possible that the global obesity epidemic may in part explain the high prevalence of hypovitaminosis D worldwide, fat constituting a large storing compartment. Hypovitaminosis D is most notable in Australia, India, Asia, Africa, South America, and surprisingly the Middle East, despite its plentiful sunshine [6,7]. Serum 25-hydroxyvitamin D (25-OHD) is the index of vitamin D nutritional status; and in addition to obesity, risk factors for low 25-OHD levels include extremes of age, female sex, winter season, low socioeconomic status, malnutrition, covered clothing style, and dark skin [5,6]. Vitamin D receptors (VDRs) are expressed in multiple tissues and cells, and the pleiotropic effect of vitamin D on nonskeletal outcomes has become increasingly recognized [5,8]. Low 25-OHD levels are associated with an increased risk of cardiovascular disease, type 2 diabetes mellitus, hypertension, MetS, autoimmune disorders, and certain types of cancer, and predict overall and cardiovascular mortality [9-22]. Vitamin D may exert its effect directly through a direct effect on gene modulation or activation of VDRs, or indirectly through regulation of calcium signaling [5,23]. Although biological plausibility for a key role of vitamin D in the above diseases is for the most part supported through well-described physiologic pathways in vitro and in animal studies (Fig. 1) [5,8,18,19,23-36], the data in humans currently stem mostly from association studies; and the evidence for a cause-effect relationship therefore remains sorely lacking.

Two recently published systematic reviews/meta-analyses examined the relationship between vitamin D levels and cardiometabolic outcomes [37,38]. Both reviews covered the literature from the late 1960s until 2009 and analyzed results from 28 and 32 studies, respectively, with overlap in the studies reviewed. Whereas association studies yielded positive results, those from randomized trials were disappointingly negative. In the meta-analysis of 28 independent studies using random effect models, Parker et al [38] showed a 43% decrease in cardiometabolic disorders. There were a significant 24% to 70% decrease in the risk of cardiovascular diseases in 11 of 16 studies, a significant 64% to 82% decrease in the risk of diabetes in 4 of 9 studies, and a 53% to 67% decrease in the risk of MetS in 4 of 8 studies [38]. Pittas et al [37] evaluated data from 13 observational studies (14 cohorts) and 18 trials and implemented random effects models meta-analyses when similar data from 3 or more observational cohorts or trials were available. In 3 of 6 analyses from 4 different cohorts, a lower risk of diabetes was reported in the highest compared with the lowest vitamin D group. Similarly, lower 25-OHD level was associated with a 1.8-fold risk of incident hypertension and a 1.3- to 2-fold increased risk of incident cardiovascular diseases [37]. Conversely, there were no significant effect of vitamin D supplementation on glycemia or incidence of diabetes in 7 trials, no effect on blood pressure in the meta-analysis of 10 trials, and no effect on cardiovascular disorders in 4 trials [37]. Limitations for both meta-analyses included heterogeneity across studies, differences in assays and cutoffs used to measure and define 25-OHD risk categories, and the fact that studies mostly recruited middle-aged white subjects, therefore rendering the applicability of observations to other age and racial groups difficult. Furthermore, the doses of vitamin D used were suboptimal and did not for the most part result in desirable 25-OHD levels of greater than 30 ng/mL [7,39].

In this issue of Metabolism, Al-Daghri and colleagues [40] report the results of a prospective noncontrolled trial investigating whether correction of hypovitaminosis D in a cohort of overweight and obese adults can improve the prevalence of MetS and its components. Fifty-nine adult male and female nondiabetic Saudis, with a mean age of 38 (±14) years and a
mean body mass index of 29 (±9) kg/m², were advised to expose themselves to sunlight for 5 to 30 minutes twice a week (before 10:00 AM and/or after 3:00 PM) and to follow a vitamin D–enriched diet for 1 year. Mean serum 25-OHD level increased from 18 nmol/L (7.2 ng/mL) to 28 nmol/L (11.2 ng/mL); and with such intervention, there was a concomitant significant decrease in the prevalence of MetS from 25% to 13% based on the modified National Health and Nutrition Examination Survey Adult Treatment Panel III definition. The latter was largely due to a parallel decrease in the prevalence of low high-density lipoprotein (HDL) cholesterol from 93% to 57% (P = .004) and of high triglycerides from 28% to 24% (P = .023). Mean HDL level rose from 0.7 to 1.05 nmol/L (P < .05), and there was a trend for a decrease in body mass index and both systolic and diastolic blood pressure. Limitations of the study included its noncontrolled, nonrandomized nature; its small sample size; the lack of adjustment for adiposity, physical activity, and phase of menstrual cycle; and the lack of an accurate assessment of exogenous vitamin D consumed and sun exposure received. Furthermore, the mean 25-OHD level reached was suboptimal, a limitation that may have further jeopardized the possibility of unveiling a significant effect of vitamin D on fuel and lipid metabolism. Nevertheless, the investigators are to be commended for conducting the study in a high-risk group for low vitamin D and MetS, a group that is representative of populations in the Middle East region, a region that registers some of the highest rates for type 2 diabetes mellitus, and for attempting to raise vitamin D levels using lifestyle modifications through diet and sunshine. Whereas pathways for the putative beneficial effect of vitamin D on components of the MetS such as blood pressure and glucose metabolism are well defined [18,23], those on lipid and fat metabolism are much less clear (Fig. 1) [5,8,18,19,23-36]. Suggested pathways for a beneficial effect on lipids include increments in hepatocellular calcium reducing triglyceride formation; stimulation of ApoA1 via the VDR, thus stimulating reverse cholesterol transport and raising HDL [30]; and an indirect effect through PTH suppression, thus enhancing lipoprotein lipase activity and triglyceride clearance. Both increments and decrements in lipid absorption have been suggested [28,29], but the former is more plausible as illustrated in Fig. 1 [32]. Vitamin D has been shown to regulate adipocyte differentiation via VDR [31] and possibly modulate adiponectin and leptin gene expression [35], the former through downregulation of tumor necrosis factor–α [24]. Whereas, in the mice model, KO of VDR or CYP27b1 leads to an obesity-resistant strain, the picture in humans is less clear [32,35,36]. The putative beneficial effect of vitamin D on fat may also positively impact glycemic index, in view of adiponectin’s effect role on insulin sensitivity [32].

A close examination of individual randomized controlled trials investigating the effect of vitamin D supplementation (calcium) on components of the MetS reveals negative findings for most trials, with the exception of the few that used high doses of vitamin D in high-risk individuals (Table [17,23,40-53]. Mitr et al [41] demonstrated in a 16-week trial that vitamin D₃ at 2000 IU/d improved insulin secretion and had a marginal effect on attenuating the rise in hemoglobin A1c (HbA1c) in obese adults at risk of type 2 diabetes mellitus. Von Hurst et al [42] showed in a 6-month trial conducted in Asian women with insulin resistance that vitamin D₃ at 4000 IU/d improved insulin resistance. Nappgal et al [43] demonstrated in a 6-week randomized trial that vitamin D₃ administration at 3 fortnightly doses of 120 000 IU resulted in an improvement in postprandial insulin sensitivity in men with baseline insulin resistance. Finally, in post hoc analyses using sera stored from an osteoporosis trial, Pittas et al showed that calcium supplementation at 500 mg/d with 700 IU vitamin D₃ per day prevented the rise in fasting glucose and resulted in a lower increment in homeostatic model assessment of insulin resistance (HOMA-IR) index in individuals with impaired fasting glucose at study entry [23]. Furthermore, short-term supplementation of elderly postmenopausal women with 800 IU of vitamin D₃ along with calcium raised serum 25-OHD by 72% and significantly decreased systolic blood pressure by 9% (P = .02) [44]. A search of the clinical trials Web site, www.clinicaltrials.org, reveals more than 85 trials investigating the effect of vitamin D supplementation on cardiovascular diseases and diabetes. Three are specifically investigating the impact of vitamin D supplementation on components of the MetS using vitamin D doses equivalent to or exceeding 2000 IU/d for a duration of 4 to 6 months in 40 to 200 individuals per trial, but only one study is enrolling subjects with MetS (accessed on November 16, 2011). The National Institutes of Health–sponsored VITAL study is enrolling 20 000 healthy subjects to investigate the impact of 2000 IU vitamin D₃, omega 3, or both on cancer and cardiovascular disorders, with measurements of various surrogate intermediary markers of NCDs.

Cardiometabolic disorders in general and MetS in particular are major causes of mortality and morbidity worldwide; hypovitaminosis D is particularly prevalent in obese individ-

### Table – Effects of vitamin D (± calcium) supplementation on various components of MetS in randomized controlled trials (1966-October 2011)

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>Patients’ age/N</th>
<th>Study design/duration</th>
<th>Dose and vitamin D used</th>
<th>Outcomes of interest</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive studies</strong></td>
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<tr>
<td>Mitri et al AJCN 2011</td>
<td>N=92 men and women at risk of type 2 diabetes mellitus Age ≥40 y</td>
<td>2×2 factorial design, double-masked placebo-controlled randomized trial 16 wk</td>
<td>2000 IU/d VitD3 and 800 mg Ca 2000 IU/d VitD3 and placebo Placebo and 800 mg Ca Placebo and placebo</td>
<td>Primary: mean change at 16 wk in disposition index (AIR g × Si), which is the product of insulin secretion and insulin sensitivity. Secondary: change at 16 wk in AIRs, Si, and glucose tolerance (HbA1c, FPG, and 2-h postload plasma glucose).</td>
<td>Disposition index (AIR g × Si) changed by a mean of 300 ± 130 in D group compared with −126 ± 127 in non-D group (P = .011). Insulin secretion changed by a Δ of 62 ± 39 mU L⁻¹ min in D group and −36 ± 37 mU L⁻¹ min in non-D group (P = .046). Marginal attenuation of the rise in HbA1c by a mean of 0.06% ± 0.03% in D group compared with 0.14% ± 0.03% in non-D group (P = .081).</td>
</tr>
<tr>
<td>Von Hurst et al British Journal of Nutrition 2010</td>
<td>N=81 Asian women with insulin resistance Age 23-68 y (42 in intervention group and 39 in PBO group)</td>
<td>Double-blind, placebo-controlled, randomized trial 6 mo</td>
<td>4000 IU/d VitD3 vs placebo</td>
<td>Primary: insulin sensitivity and levels. Secondary: lipid profile and CRP.</td>
<td>Significant difference in the change in HOMA1-IR between groups (P = .03), with a decrease of −0.25 (0.24, −0.81) in the vitamin D–supplemented group and an increase of 0.36 (1.16, −0.41) in the placebo group. FPG, CRP, total cholesterol, TG/HDL cholesterol ratio, HDL cholesterol did not differ between groups. Improvement of OGIS by a mean difference of 30.06 ± 15.42 mL min⁻¹ kg⁻¹ between supplemented group and control group (P = .055). Blood pressure, lipid profile, HOMA, and QUICKI insulin sensitivity index unchanged.</td>
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<tr>
<td>Nagpal et al Diabetic Medicine 2009</td>
<td>N=100 men Age ≥35 y</td>
<td>Double-blind, placebo randomized controlled trial 6 wk</td>
<td>3 doses of 120 000 IU VitD3 fortnightly vs placebo</td>
<td>Primary: OGIS index. Secondary: Δ blood pressure, Δ lipid profile, Δ function HOMA, QUICKI.</td>
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<tr>
<td>Pittas et al Diabetes Care 2007</td>
<td>N=314 men and women Age ≥65 y</td>
<td>Post hoc analyses from an osteoporosis double-blind, randomized controlled trial 3 y</td>
<td>500 mg Ca and 700 IU VitD3 vs placebo</td>
<td>Primary: FPG and glucose tolerance. Secondary: HOMA-IR, CRP, interleukin-6.</td>
<td>Ca/VitD3 prevented increases in plasma glucose and insulin resistance in patients with impaired fasting glucose. The mean change in FPG in placebo group was 0.34 ± 0.11 mmol/L compared with 0.02 ± 0.09 mmol/L in Ca/D group (P = .042). HOMA-IR increased in placebo arm by 0.91 ± 0.31 mmol/L compared with 0.05 ± 0.19 mmol/L in Ca/D group (P = .031). No effect on markers of systemic inflammation.</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Findings</td>
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<tr>
<td>Pfeifer et al, <em>JCEM</em> 2001</td>
<td>N=148 women</td>
<td>Double-blind, randomized controlled trial 8 wk</td>
<td>1200 mg Ca and 800 IU VitD3 1200 mg Ca</td>
<td>Blood pressure Supplementation with VitD3 and Ca reduced systolic blood pressure from 144.1 ± 20.4 to 131 ± 16.9 mm Hg (P = .02).</td>
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<tr>
<td>Rajpathak et al, <em>AJCN</em> 2010</td>
<td>N=1259 women</td>
<td>Randomized, double-blind, controlled trial (Women's Health Initiative trial) 5 y</td>
<td>1000 mg Ca and 400 IU VitD3 vs placebo</td>
<td>Change in lipids levels No significant effects of Ca/D supplementation on changes in circulating lipids.</td>
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<tr>
<td>Daly et al, <em>EJCN</em> 2009</td>
<td>N=167 men</td>
<td>Randomized controlled trial 2 y</td>
<td>1000 mg Ca and 800 IU VitD3 vs placebo</td>
<td>Weight, systolic or diastolic blood pressure, total cholesterol, HDL, LDL, triglyceride No beneficial effect on blood pressure, lipid, or lipoprotein concentrations in older men.</td>
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<tr>
<td>Jorde et al, <em>Internal Med</em> 2010</td>
<td>N=438 men and women</td>
<td>Double-blind, randomized controlled trial 1 y</td>
<td>500 mg/d Ca and VitD3: 40 000 IU/wk 500 mg/d Ca and VitD3: 20 000 IU/wk 500 mg/d Ca and placebo</td>
<td>Fasting serum lipid, blood pressure, 75-g oral glucose tolerance test. No effect of vitamin D supplementation on glucose tolerance, blood pressure, or lipid profile.</td>
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<tr>
<td>Sneve et al, <em>European Journal of Endocrinology</em> 2008</td>
<td>N=445 men and women</td>
<td>Double-blind, randomized controlled trial 12 mo</td>
<td>500 mg/d Ca and VitD3: 40 000 IU/wk 500 mg/d Ca and VitD3: 20 000 IU/wk 500 mg/d Ca and placebo</td>
<td>Weight reduction No significant reduction in total weight, percentage fat mass, or change in fat distribution as evaluated by the waist-hip ratio.</td>
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<tr>
<td>De Boer et al, <em>Diabetes Care</em> 2008</td>
<td>N=33951 women</td>
<td>Double-blind, randomized controlled trial (Women's Health Initiative trial) 7 y</td>
<td>1000 mg Ca and 400 IU VitD3 vs placebo</td>
<td>Change in fasting glucose, insulin, and HOMA-IR measurements over time by calcium/D treatment assignment and baseline FPG concentration Ca and VitD3 supplementation did not reduce the risk of developing drug-treated diabetes.</td>
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<tr>
<td>Margolis et al, <em>Hypertension</em> 2008</td>
<td>N=3212 women</td>
<td>Randomized, double-blind, placebo-controlled trial (Women's Health Initiative trial) 7 y</td>
<td>1000 mg Ca and 400 IU VitD3 vs placebo</td>
<td>Blood pressure and the incidence of hypertension Ca and VitD3 supplementation did not reduce either blood pressure or the risk of developing hypertension. Consumption of Ca + VitD3 during a weight loss intervention enhanced the beneficial effect of body weight loss on the lipid and lipoprotein profile in overweight or obese women with usual low daily calcium intake.</td>
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<tr>
<td>Major et al, <em>AJCN</em> 2007</td>
<td>N=63 women overweight or obese Mean age 43.6 ± 5 y</td>
<td>Double-blind, randomized controlled trial 15 wk</td>
<td>1200 mg Ca and 400 IU VitD3 vs placebo</td>
<td>Change in lipids levels, glucose-insulin profile, blood pressure, and weight loss Ca and VitD3 supplementation did not reduce either blood pressure or the risk of developing hypertension. Short-term oral administration of supraphysiological doses of calcitriol has no effect on insulin sensitivity in healthy subjects. No effect in fasting or stimulated glucose tolerance. 1-kg decrease in weight in treated group (P &lt; .05).</td>
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<td>Fiser et al, <em>European Journal Clin Invest</em> 1997</td>
<td>N=18 men Mean age 26 ± 3 y</td>
<td>Double-blind, randomized controlled trial 7 d</td>
<td>1.5 µg of calcitriol per day vs placebo</td>
<td>Insulin-mediated glucose uptake and insulin sensitivity Short-term oral administration of supraphysiological doses of calcitriol has no effect on insulin sensitivity in healthy subjects.</td>
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<td>Ljunghal et al, <em>Acta Med Scand</em> 1987</td>
<td>N=65 men Age 61-65 y</td>
<td>Block-randomized, placebo-controlled, double-blind trial 12 wk</td>
<td>0.75 µg/d of 1α-hydroxycalciferol vs placebo</td>
<td>FPG, HbA1c, insulin resistance No effect in fasting or stimulated glucose tolerance. 1-kg decrease in weight in treated group (P &lt; .05).</td>
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(continued on next page)
uals. The VDR is expressed in many relevant target tissues, and ample data support biological plausibility for a key role of vitamin D on several components of the MetS. The evidence available to date from cross-sectional or small longitudinal studies, the suggestive evidence provided in the trials detailed above, and the significant decrease in the prevalence of MetS in the study of Al Daghri et al are intriguing and well deserving of further investigations. Enrollment of at-risk individuals and selection of high doses of vitamin D (without calcium) and of a study design with adequate power and sufficient duration are critical factors to conclusively resolve the uncertainties regarding a putative beneficial role of vitamin D per se on the MetS and its components. If this hypothesis is unequivocally proven, vitamin D supplementation would provide a formidable, safe, and affordable strategy to address a growing and costly major public health problem.

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Conflict of Interest

The author declares no conflict of Interest.

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REFERENCES


Von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient—a randomized, placebo-controlled trial. Br J Nutr 2010;103:549-55.


