hormone concentrations. Moreover, for each 10 ng/ml (25 nmol/l) decrease in 25(OH)D concentration, the fracture risk increased by 33% [12]. Moreover, vitamin D deficiency is also associated with decreased bone mineral density (BMD) in postmenopausal women, independently of ethnic origin [13,14].

3.1.2. Interventional studies

Evidence from RCTs suggests that vitamin D supplementation may reduce fracture risk only when combined with calcium [15]. An umbrella review of meta-analyses of RCTs showed that calcium at doses of 500–1200 mg/day, combined with vitamin D at doses of 400–1600 IU/day (10–40 μg/day), reduced the risk of hip fractures in eight of 12 meta-analyses (RR from 0.61 to 0.84) and the risk of any fractures in seven of 11 meta-analyses (RR from 0.74 to 0.95) with a follow-up of 1–7 years. However, no fracture risk reduction was noted in meta-analyses evaluating community-dwelling individuals exclusively [16]. This was also confirmed in the recent Vitamin D and Omega-3 Trial (VITAL), the largest and most holistic RCT so far in this context, in which vitamin D monotherapy, at a dose of 2000 IU/day, had no effect on fracture risk, in men >50 and women >55 years of age [17]. In any case, the anti-fracture benefit of the combination of vitamin D with calcium is mostly evident in the elderly populations [15].

A U-shaped effect of vitamin D supplementation on fracture risk should also be considered, since high vitamin D doses, at monthly (60,000–100,000 IU) or daily intervals (>4000 IU), tend to increase fracture risk, mainly in individuals without vitamin D deficiency [15]. This may be attributed to the functional decline of lower extremities and increased risk of falls [18]. On the other hand, a meta-analysis of 11 RCTs for the primary prevention of fractures in adults without vitamin D deficiency, osteoporosis or prior fracture did not find any benefit of vitamin D supplementation, in doses ranging between 300 IU/day and 100,000 IU/month [19].

Calcium can also be provided through the consumption of dairy products (a supplement of 500 mg is equivalent to eating 2 - 3 portions of dairy products). Interestingly, increased consumption of dairy products is associated with a reduced risk of hip fractures [20]. Calcium supplementation at daily doses of up to 1000 mg/day is safe regarding cardiovascular risk [21,22]. However, excessive calcium supplementation (>1000 mg) may be associated with gastrointestinal complaints and urinary calculi [19].

Studies have been inconsistent in the findings concerning an association between vitamin D and BMD [23,24]. Nevertheless, vitamin D (100–1600 IU/day), when combined with protein (10–44 g/day), may improve muscle strength in patients with sarcopenia, according to a recent meta-analysis of eight RCTs. This effect was pronounced in patients with severe vitamin D deficiency [<12 ng/ml (<30 nmol/l)] [25].

3.1.3. Summary recommendations

There is no evidence for an anti-fracture benefit of vitamin D supplementation in postmenopausal women without vitamin D deficiency or at low fracture risk. In contrast, vitamin D supplementation combined with calcium should be considered in postmenopausal women of any age with low serum 25(OH)D concentrations (<20 ng/ml or <50 nmol/l) suffering from osteoporosis and/or at high fracture risk, according to the FRAX model. A tailor-made approach that takes account of BMI, adherence and compliance with treatment is recommended, with regular assessment (3–6 monthly intervals) to check that 25(OH)D concentrations exceed the threshold of 20 ng/ml (50 nmol/l) and maintain it. This is usually achieved by daily doses of 2000–4000 IU (4000–6000 IU in obese patients) [4]. In parallel, 1000–1200 mg of calcium, either from dietary sources or from supplements, should be encouraged for at least 3–5 years to obtain the optimal benefit for skeletal health. This daily allowance of calcium does not increase the risk of cardiovascular disease or nephrolithiasis.

3.2. Cardiovascular disease

3.2.1. Epidemiological studies

Cross-sectional and cohort studies support an association between vitamin D deficiency and the prevalence of cardiovascular risk factors, such as hypertension, dyslipidemia, hyperglycemia and metabolic syndrome in the general population [26]. A meta-analysis of 10 prospective (n = 58,262) and 19 cross-sectional studies (n = 90,535) showed a lower risk of hypertension with 25(OH)D concentrations in the highest compared with the lowest category [RR 0.76 (95% CI 0.63–0.90) and 0.79 (95% CI 0.73–0.87), for prospective and cross-sectional studies, respectively]. However, this was evident for women ≤55 years, but not for older ages [27]. This finding was replicated in a cross-sectional analysis of the National Health and Nutrition Examination Surveys (NHANES) 2007–2010, where no association was observed in postmenopausal women [28]. A meta-analysis of 57 cross-sectional (n = 210,575) and two cohort studies (n = 8494) confirmed the protective effect of highest vs. lowest 25(OH)D concentrations on triglycerides [odds ratio (OR) 0.81, 95% CI 0.74–0.89], irrespective of age. This was also the case for high-density lipoprotein cholesterol (HDL-C) (OR 0.82, 95% CI 0.76–0.89). There was no association between 25(OH)D concentrations and total (TC) or low-density lipoprotein cholesterol (LDL-C) [29]. Concerning glucose metabolism, an inverse association exists between vitamin D status and insulin resistance [30]. Meta-analyses have also demonstrated an increased risk of type 2 diabetes in patients with vitamin D deficiency compared with those with sufficiency [31,32]. Furthermore, vitamin D deficiency is also associated with an increased risk of metabolic syndrome in postmenopausal women, irrespective of estradiol concentrations [33].

A growing body of evidence shows an inverse association between 25(OH)D concentrations and the prevalence of CVD, including coronary heart disease and stroke, and CVD mortality. This is most evident in the case of severe vitamin D deficiency [25(OH)D <10 ng/ml (<25 nmol/l)] [34]. A meta-analysis confirmed a higher incidence of major adverse cardiovascular events (OR 1.92, 95% CI 1.24–2.98) for patients with vitamin D deficiency [35]. Severe vitamin D deficiency is associated with increased cardiovascular mortality in older adults, according to another meta-analysis (RR 1.47, 95% CI 1.15–1.81) [36]. This was confirmed in a prospective study from the UK Biobank, which examined 307,601 participants of White European ancestry (aged 37–73 years at enrolment) [37].

3.2.2. Interventional studies

Vitamin D supplementation may have a modestly beneficial effect on lipid profiles in postmenopausal women. A meta-analysis of RCTs showed a decrease in triglyceride concentrations [weighted mean difference (WMD) -3.55 mg/dl, 95% CI -5.34 to −1.76] with vitamin D supplementation (300–4000 IU/day). HDL-C increased when the treatment duration was <26 weeks (WMD 2.67 mg/dl, 95% CI 0.66–4.68), as did TC (WMD 6.56 mg/dl, 95% CI 0.78–12.35). Moreover, vitamin D decreased LDL-C when the dose was >400 IU/day (WMD -1.89 mg/dl, 95% CI -2.47 to −1.31) [38]. Vitamin D supplementation has no effect on systolic or diastolic blood pressure, independent of age, baseline vitamin D status or vitamin D dose [39]. On the other hand, vitamin D supplementation may improve the metabolic syndrome profile in postmenopausal women, especially triglycerides and insulin resistance [40], although it has no effect on body composition and weight [41]. It may also reduce the incidence of type 2 diabetes in patients with prediabetes by 11% (RR 0.89, 95% CI 0.80–0.99), according to another meta-analysis [42], especially in non-obese patients and with daily doses ≥2000 IU [42]. However, vitamin D supplementation (from 400 to 100,000 IU/month) does not reduce the risk of total cardiovascular events, myocardial infarction, stroke, and cardiovascular or all-cause mortality, according to several meta-analyses [43–45] and the VITAL study [17].