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INCREASE IN VITAMIN D PRESCRIPTIONS IN A SOUTHERN ITALY REGION OVER 2011-2015 PERIOD

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SUMMARY

Cholecalciferol is the main dietary form of vitamin D. Its synthesis depends on the intensity of the ultraviolet radiation. Since endogenous vitamin D levels are often low and food is naturally poor of all forms of vitamin D, supplementary treatment need to be frequently prescribed from physicians. Serum levels of 25-hydroxyvitamin D, the main circulating vitamin D metabolite, determine the range of vitamin D insufficiency and deficiency, as 20-13 ng/ml and less than 12 ng/ml, respectively.

The aim of the present study was to analyze changes in prescribing pattern of vitamin D in a region of the Southern Italy (Basilicata). We examined the trend in the vitamin D prescription, by age and gender, over the period 2011 to 2015. We classified population in three subgroups: pediatrics (0-14 years old), adults (15-65 years old and elderly (over 65 years old).

Our results showed a yearly marked increase of Vitamin D prescription for all three age groups, in both sexes. Moreover, in adult and older women there was a higher increase in terms of number of patients, sum of dispensed boxes and total costs compared to men.

In conclusion, we gave an overview on the use of vitamin D supplementation in Basilicata, from 2011 until 2015, indicating an extensive annual increase of its prescription, particularly in adult and older women.

Key words
Vitamin D; prescription; age; gender; supplementation.

Impact statement
Our study evidenced a yearly increase of vitamin D prescription, in particular in adult and older women from Basilicata region.

INTRODUCTION

Cholecalciferol (also known as vitamin D3, the main dietary form of vitamin D) is produced from 7-dehydrocholesterol (1). The only organ able to synthesize the critical components of the vitamin D-signaling pathway is the skin. The synthesis depends on the intensity of the ultraviolet radiation, which is dependent on latitude and season (2). It is used by the human body according to its needs.

Cholecalciferol can also exist as pharmaceutical ingredient and it can be obtained through food (3). However, while food is naturally poor of all forms of vitamin D, marketed fortified dairy products or dietary supplements may represent a readily available source to correct states of vitamin D deficiency and target the preferred 25-hydroxyvitamin D levels, the main circulating vitamin D metabolite (4, 5). Its serum level serves as the best determinant of its

concentration, being one of the most reliable biomarkers of vitamin D status (6), even though there are still no standardized assay methods. The following ranges of 25-hydroxyvitamin D levels define conditions of insufficiency and deficiency: between 20-13 ng/ml and less than 12 ng/ml, respectively. Thus, in order to maintain the best mineral and skeletal homeostasis and to avoid rickets and osteomalacia, several guidelines recommend that serum 25-hydroxyvitamin D levels should be 20 ng/ml or above (7, 8).

It has been shown that vitamin D deficiency is quite widespread in the general population and, particularly, in at-risk subgroups of individuals (9). Specific vulnerable subgroups include pregnant and breastfeeding women, all infants and children from the age of six months until the age of five years, older persons, institutionalized, and non-western immigrants (10).

In order to direct a proper consumption of vitamin D, national scientific societies have developed specific guidelines for the definition, diagnosis, prevention and treatment of inadequate vitamin D status and osteoporosis. In Italy, guidelines were first drafted by a committee and then approved by the board of the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (11, 12). Notably, the proposed guidelines also received the endorsement of the other scientific societies that deal with bone diseases (13).

Despite this, in 2014 the Italian Medicines Agency (AIFA) issued a warning on the rise of vitamin D consumption and relative inappropriate prescriptions. In the AIFA report, vitamin D was put on a watch list, and was defined as a "special monitored drug", because of the steady growth in the sales of vitamin D and the possibility of inappropriate use by patients (The Medicines Utilisation Monitoring Centre, National Report on Medicine use in Italy. Rome, Italian Medicines Agency, 2014). Afterward, in October 2019, AIFA modified the legislation for the treatment of vitamin D insufficiency, establishing the Note 96, which regulates the reimbursement of cholecalciferol and calcifediol by the National Health System (https://www.aifa.gov.it/Nota-96). Indeed, as revealed by Euromonitor International, vitamin D market is actually considered a booming business, as it represents the fastest growing consumer health category. This was also strengthened by the economic report "Global Vitamin D Testing Market 2015-2019", in which analysts forecast the global vitamin D testing market to grow at a Compound Annual Growth Rate of 7.57% during the period 2014-2019 (http://www.researchandmarkets.com/reports/3346106/global-vitamin-d-testing-market-2015-2019).

The basis of such awesome market increase is supposed to be the growing scientific literature regarding cholecalciferol. Indeed, a search on PubMed with the keywords "cholecalciferol" or "vitamin D" showed a consistent increase in the number of published papers throughout the last ten years. Most of those investigations are linked to a variety of health benefits beyond bone and skeletal strength. In this regard, several studies have pointed out that vitamin D also acts as a hormone mediating tissue effects across a wide range of homeostatic functions. Recent research has linked vitamin D deficiency to other debilitating illnesses such as a cancer, cardiovascular diseases, multiple sclerosis, dementia, Parkinson's disease and more (14, 15).

Nonetheless, several systematic reviews have raised doubts about the utility of vitamin D use to prevent osteoporosis, whether taken alone, as well as its effects on health in general (16-19).

Along with this, it should also be taken into account that the rise in cholecalciferol prescriptions has important cost implications, which could importantly affect the sustainability of Italian public health system budget.

Thus, the aim of the present study was to analyze changes in prescribing pattern of vitamin D in a region of the Southern Italy (Basilicata). We examined the trend in the vitamin D prescription, by age and gender, over the period 2011 to 2015. These are the most recent avail-

able data, since data about 2016-2020 period will be available in 2021.

MATERIALS AND METHODS

We conducted a cross-sectional time-series analysis describing the trends in vitamin D dispensing and spending in a region of Southern Italy, Basilicata, between January 1st, 2011, and December 31st, 2015, using data from ASL Matera (Basilicata, Italy) database. Number and percentage of patients, sum of dispensed boxes and total costs were analyzed per age and gender. In terms of age, patients were classified in three subgroups: 0-14 (pediatrics), 15-65 (adults) and over 65 (elderly). To examine regional prescription trends, we used descriptive statistics and all graphs were realized by using PRISM GraphPad 6.0 software.

RESULTS

Prescription data for patients of Basilicata region, covering a five years period beginning on January 1st, 2011 and ending on December 31st, 2015, were subjected to a retrospective drug utilization observational analysis.

Subjects receiving cholecalciferol were raised from 2% of the total adult inhabitants of Basilicata in 2011 to 6% in 2015.

Figure 1 a gives a representation of the heterogeneity, in terms of age, of the patients considered in the present study. Although already in 2011 the number of treated subjects was gradually increased in an age-dependent manner, in 2015 the gap between 0-14 and 15-65 became even more evident (+ 407% in 2011; + 637% in 2015). **Figure 1 b**, **c** revealed a difference in the trend increase among age clusters in 2011 and 2015 in female respect to male subjects.

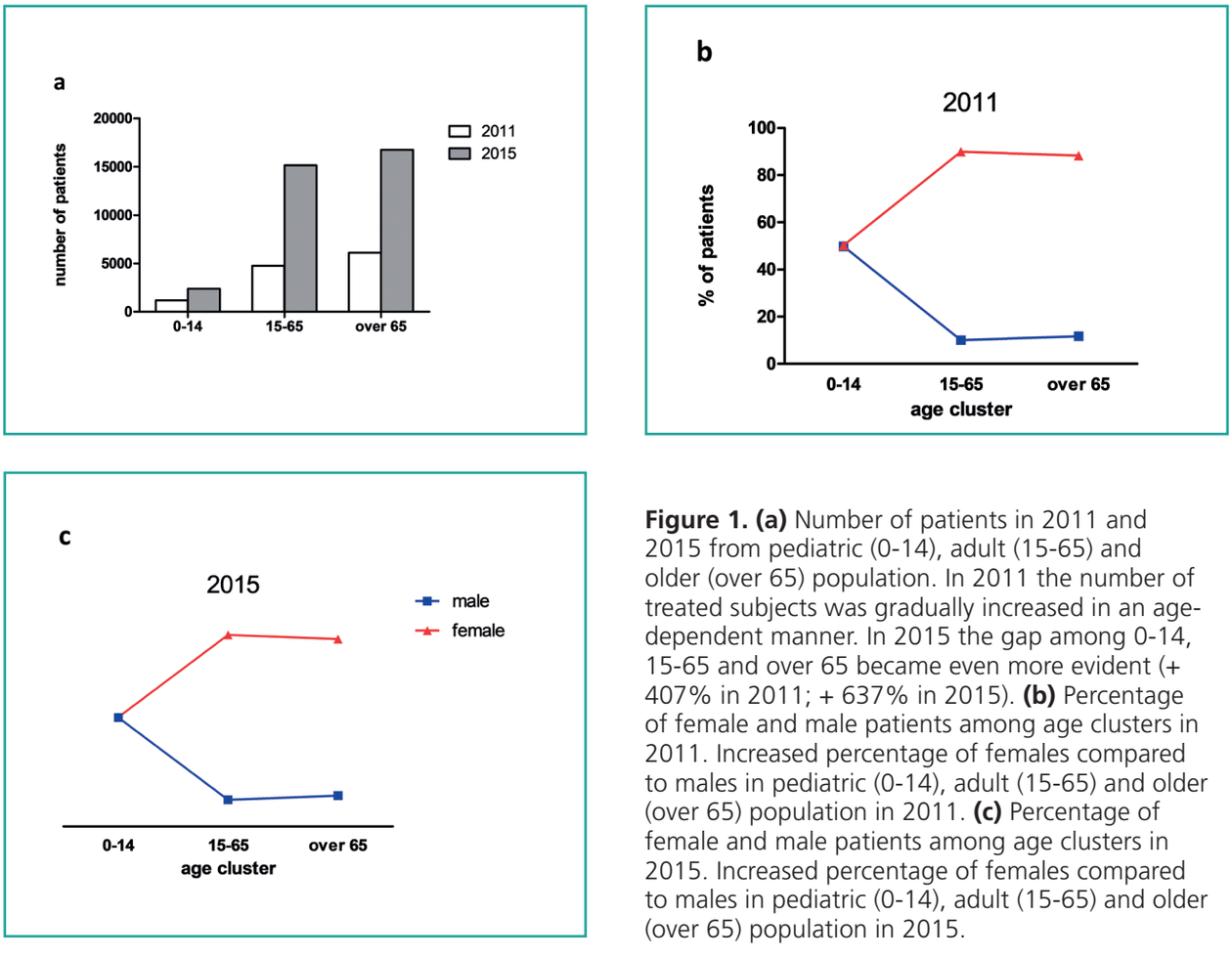

Figure 1. (a) Number of patients in 2011 and 2015 from pediatric (0-14), adult (15-65) and older (over 65) population. In 2011 the number of treated subjects was gradually increased in an age-dependent manner. In 2015 the gap among 0-14, 15-65 and over 65 became even more evident (+ 407% in 2011; + 637% in 2015). **(b)** Percentage of female and male patients among age clusters in 2011. Increased percentage of females compared to males in pediatric (0-14), adult (15-65) and older (over 65) population in 2011. **(c)** Percentage of female and male patients among age clusters in 2015. Increased percentage of females compared to males in pediatric (0-14), adult (15-65) and older (over 65) population in 2015.

Table I. Yearly number and percentage of male and female patients from 2011 to 2015.

	MALE		FEMALE	
year	Number of patients	% of patients per year	Number of patients	% of patients per year
2011	1,773	15	10,247	85
2012	2,463	16	12,685	84
2013	3,034	15	16,801	85
2014	4,095	16	22,201	84
2015	5,404	16	28,858	84

As shown in **table I**, within the range of age investigated (0-102 years), the number of patients receiving vitamin D prescriptions significantly increased, ranging from 12,020 in 2011 to 34,262 in 2015 (+ 285%). During the observed period, male patients receiving cholecalciferol were increased, ranging from 1,773 in 2011 to 5,404 in 2015 (from 15% to 16% of the total sample), while female subjects were increased, ranging from 10,247 in 2011 to 28,858 in 2015 (from 85% to 84% of the total sample).

Moreover, a total of 542,278 prescriptions was recorded in the time span considered. Among them, 64,759 (12%) prescriptions were for male patients and 477,519 (88%) for fe-

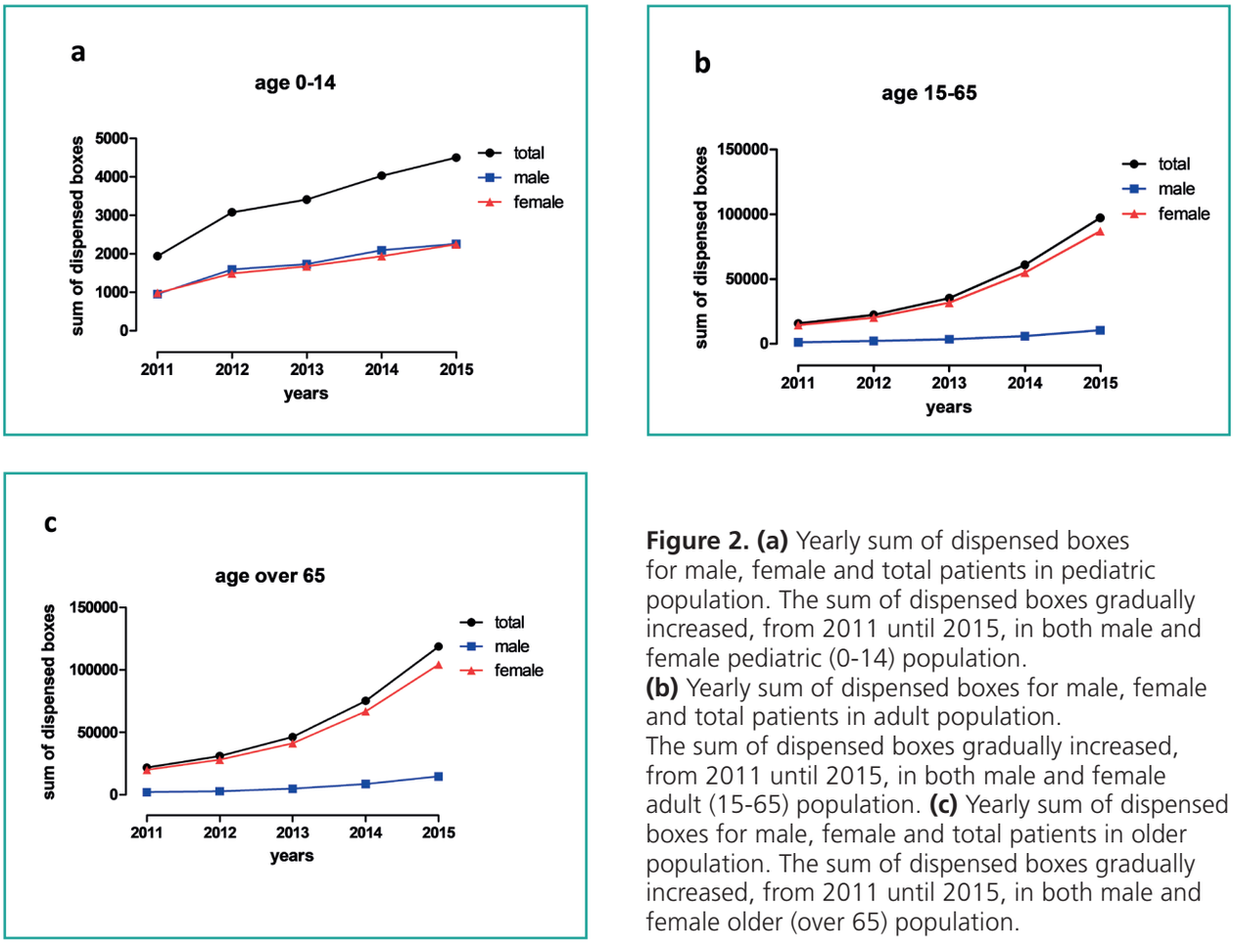

Figure 2. (a) Yearly sum of dispensed boxes for male, female and total patients in pediatric population. The sum of dispensed boxes gradually increased, from 2011 until 2015, in both male and female pediatric (0-14) population.
(b) Yearly sum of dispensed boxes for male, female and total patients in adult population.
The sum of dispensed boxes gradually increased, from 2011 until 2015, in both male and female adult (15-65) population. **(c)** Yearly sum of dispensed boxes for male, female and total patients in older population. The sum of dispensed boxes gradually increased, from 2011 until 2015, in both male and female older (over 65) population.

male patients. The total number of prescriptions strongly increased from 39,468 (2011) to 220,505 (2015) dispensed boxes (559% increase). In particular, **figure 2 a** shows the yearly patterns of prescriptions of vitamin D in the pediatric population (age 0-14) during the period of 2011-2015, assessed by sums of number of dispensed boxes. Subjects receiving cholecalciferol were 10% of the total sample in 2011 and 7% in 2015. The average number of prescriptions per pediatric patient in the whole sample was 1.81. **Figure 2 b, c** shows the yearly trend of vitamin D prescriptions in adult (age 15-65) and in older population (age over 65), during the period 2011-2015, respectively. Although prescriptions were similar among sexes in 0-14 years age range (**figure 2 a**), a gender-dependent effect became evident both in 15-65 years age range (**figure 2 b**) and in over 65 group (**figure 2 c**). The average number of prescriptions per patient in the whole sample was 5%. Overall, the prevalence of cholecalciferol use increased with age in both genders in all considered years (2011-2015). The highest prevalence in 2015, 13.5%, was found in age cluster over 65 (**figure 2 c**). In women, the absolute increase was steep starting with 14,508 dispensed boxes in 2011 to 86,863 dispensed boxes in 2015 in the 15-65 age group, with a 499% growth, whereas in men a more gradual increase was observed (**figure 2 b**). Likewise, in the over 65 age group, a 426% increase was retrieved in women, and a less sudden rise was observed in men (**figure 2 a**).

A cost analysis was also performed. In particular, in the period 2011-2015 we found a gradual increase in total costs for cholecal-

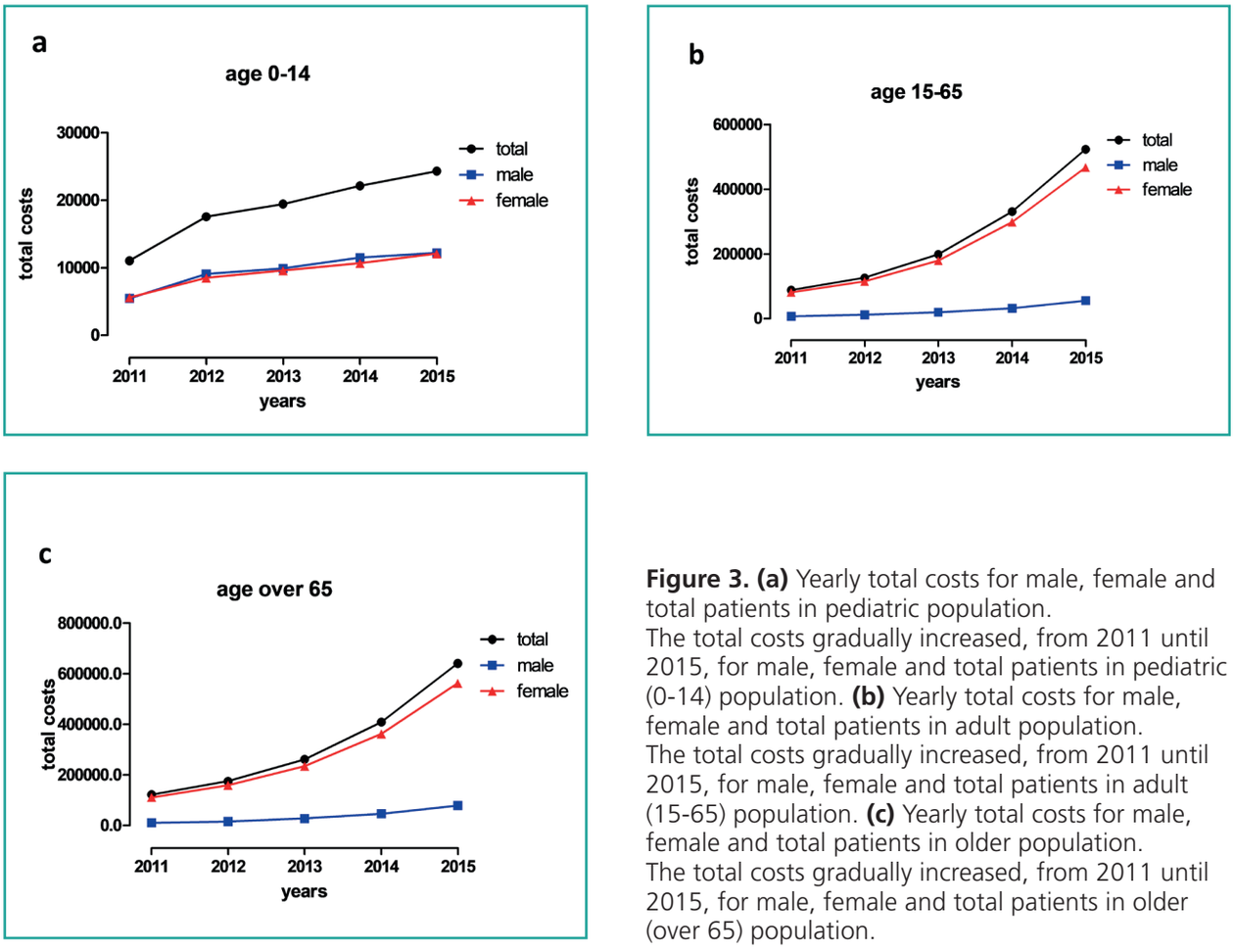

Figure 3. (a) Yearly total costs for male, female and total patients in pediatric population.
The total costs gradually increased, from 2011 until 2015, for male, female and total patients in pediatric (0-14) population. **(b)** Yearly total costs for male, female and total patients in adult population.
The total costs gradually increased, from 2011 until 2015, for male, female and total patients in adult (15-65) population. **(c)** Yearly total costs for male, female and total patients in older population.
The total costs gradually increased, from 2011 until 2015, for male, female and total patients in older (over 65) population.

ciferol prescriptions in the age cluster 0-14, whereas for the age cluster 15-65 and over 65 the increase in total costs was more pronounced (**figure 3**). Indeed, while for the age 0-14 the increase from 2011 to 2015 in total costs was around 120% (**figure 3 a**), for 15-65 and over 65 age such a rise was 494% and 424%, respectively (**figure 3 b, c**). The *pro capite* expenditure was € 0.38 in 2011 to move to € 2.06 in 2015, thus registering a 442% of increase. This escalation in the costs was indeed related to the increase in prescription number taking into account that the price of 100,000 UI package of cholecalciferol was almost constant across years (€ 5.7 in 2011 and € 5.42 in 2015).

DISCUSSION

In this study, we analyzed vitamin D prescription data in Basilicata, a Southern Italy region, from 2011 until 2015, with respect to gender and age. We found an elevation in the number of patients related to age increase. Indeed, there was an increase in the number of adult patients compared to pediatric subjects and the number of patients over 65 further increased in respect to adults and pediatrics. All three age groups showed an increase in the number of patients in 2015 compared to 2011. In good agreement with our observations, previous studies reported a worldwide marked increase in Vitamin D prescription in the last decade (20). This could be due to an overzealous correction of vitamin D deficiency actuated by physicians, often without the previous assessment of its deficiency (21). Indeed, circulating 25-hydroxyvitamin D concentration is the best indicator of vitamin D status and it is nowadays rapidly measured in many laboratories (22).

Moreover, the percentage of female patients was the same as males in pediatric population, but in adults and elderly, the females' percentage was considerably higher in respect to males. Confirming the result related to the number of patients, we report a constant annual increase in the sum of dispensed boxes in all the three groups of age, with a marked increase in adult and older females. Indeed, vitamin D deficiency is a global problem well recognized in Europe, with females at particular risk (23). Beyond childhood, young women, especially during pregnancy, often occur in severe vitamin D deficiency, with higher risk with advancing age in a woman's lifecycle (14). Moreover, in addition to the classical musculoskeletal functions, vitamin D is showing to have emerging non-classical effects in various pathologies, such as cancer, multiple sclerosis, hypertension, cardiovascular disease, obesity, psoriasis, and psychiatric diseases (14, 15), as well as to be involved in reproductive and endocrine fields (24). Furthermore, recent studies are investigating the influence of vitamin D in people with coronavirus disease (Covid-19). Different observational studies found an association between vitamin D deficiency and Covid-19 severity (25-27). Indeed, it has been hypothesized a possible role for vitamin D in the reduction of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), acting by diminishing the inflammatory cytokines production and the virus replication, and maintaining the endothelial integrity (25).

As a result, vitamin D has a key role to maintain health status, denoting several beneficial effects beyond bone. In order to reach its sufficiency, vitamin D supplementation is commonly required (28).

On the other hand, oversupply can be as harmful as undersupply. Excessive vitamin D supplementation can lead to serious complications regarding its toxicity. Vitamin D toxicity is almost always an iatrogenic problem that can be life-threatening whether underestimated or not diagnosed (29). Hypervitaminosis D is directly followed by hypercalciuria and later by hypercalcemia, which can result lethal, especially in elderly. An interesting review summarized several case reports about vitamin D overdose and intoxication (30). In particular, patients, showing serum vitamin D concentrations ranging between 150 and 1220

ng/mL and serum calcium concentrations between 11.1 and 23.1 mg/dL, reported severe consequences, including nausea, vomiting, weakness, polyuria, nephrocalcinosis, and renal failure (31). Intriguingly, high concentration ranges were reached mainly because most of the patients received intramuscular injections of vitamin D containing very high dose at frequent intervals (daily to weekly). In fact, parenteral administration of vitamin D should be avoided unless there is evidence of malabsorption (21).

Hence, to prevent vitamin D toxicity, awareness needs to be done among healthcare providers in order to avoid irrational use of vitamin D in mega-doses (21). Recently, in Italy, in order to monitor vitamin D prescriptions and total costs, the Italian Medicine Agency (AIFA) adjusted vitamin D legislation and restricted prescriptions to particular clinical cases or when 25-hydroxyvitamin D concentrations are less than 20 ng/ml (https://www.aifa.gov.it/Nota-96). Following the trend of the other parameters, also the total costs for vitamin D in Basilicata annually increased, showing sex differences only in adults and elderly. In particular, total costs for adult and older females were consistently higher compared to males. In line with our results, the annual increase in total costs reimbursement by the Regional Health System for vitamin D-related compounds was also indicated for Tuscany region (1). Although authors showed gender combined data, they also reported a higher percentage of prescriptions among women (1). In this regard, massive literature demonstrated that postmenopausal women are often exposed to sarcopenia and osteoporosis risk, since menopause is associated with a natural decline in estrogen levels, with a progressive decrease of muscle strength and bone density (32). Accordingly, it has been reported that the risk of an osteoporotic fracture at age 50 is around 40-53 % in women and 13-22 % in men from Western countries (33).

Very recently, an AIFA report has communicated a reduction of vitamin D total costs of about 30% compared to previous periods, due to the Note 96 release (https://www.aifa.gov.it/-/vitamina-d-consumi-e-spesa-ridotti-dall-introduzione-della-nota-96). The emerging hypothesis showing the involvement of vitamin D deficiency in the outcome of Covid-19 patients (25-27), especially in the over 65 age group, raises impacting concerns, thus requiring deeper and more extensive investigations.

CONCLUSIONS

To conclude, our retrospective drug utilization study gave an overview on the use of vitamin D supplementation in Basilicata, from 2011 until 2015, indicating an extensive annual increase of its prescription, particularly in adult and older women.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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