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# Dietary supplement use among patients with chronic kidney disease

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**Background. Dietary supplements (DS) are available over the counter, but patients with impaired renal function are specifically at risk for toxicity when consuming certain DS. The aim of this study was to evaluate the prevalence and characteristics of DS use in patients with chronic kidney disease (CKD). Material and methods. A cross-sectional, controlled DS use survey (22 questions) was conducted among 180 CKD patients (stage 1–5, dialysis, kidney transplant), with 60 patients without CKD serving as controls. Results. DS use did not differ significantly between subjects with and without CKD, unless the CKD patients were on dialysis. In the CKD group, 20% admitted to use DS regularly and 22% did not take the mat all. In the controls, DS consumption was 17% and 13%, respectively (NS). The DS use was higher among women ascompared to men (89% *vs*. 70%; $p < 0.005$), and people living in cities *versus* those living in the country side (81% *vs*. 63%; $p < 0.05$). DS most commonly used were: vitamins, minerals, and herbs. Major indications for DS use included: musculoskeletal issues, general health improvement and prevention of urinary tract infections. Subgroup analyses revealed that dialysis patients were characterized by a significantly higher DS use in comparison to CKD stage 1–5 subjects and renal transplant recipients. The decision to introduce DS was made by the physician in 54% of cases; by a pharmacist in 9% of cases, and by the patients themselves in 37%. Only 21% of patients with CKD, and 27% of subjects without CKD, declared knowledge of any possible side-effects associated with DS (NS). Conclusions. The use of DS among patients with CKD is similar to patients without CKD, with the exception of those on dialysis. Vitamins and minerals were the most commonly reported DS consumed. The knowledge on potential side-effectof DS was limited to approximately one-fourth of those surveyed.**

**Key words**: dietary supplements, vitamins, minerals, chronic kidney disease, dialysis, toxicity

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**Abbreviations**: DS, dietary supplements; CKD, chronic kidney disease; CKDND, non-dialysis dependent CKD; CKDD, dialysis subjects; CKDT, patients after kidney transplantation

## INTRODUCTION

Dietary supplements (DS) are food products that contain concentrated vitamins, minerals, or other substances with a nutritional or physiological value. Initially, they were developed for individuals with micronutrient deficiencies that could not be corrected with a normal diet.

Consumption has grown among the general population, with the major indications for taking them being: maintaining good health and prevention of numerous diseases. Intense mass media marketing advertising DS as safe products with proven therapeutic potential, together with the widespread over-the-counter availability, have led to an enormous popularity of DS in the general population, as well as in various patient groups. The Food and Drug Administration estimates the number of DS products in the United States to exceed 55000 based on the National Institutes of Health 'Dietary Supplement Label Database' found online at https://www.dsld.nlm.nih.gov/dsld/index.jsp. Over 50% of the American general population consumes at least one DS daily (Wallace *et al.,* 2014).In Poland, the DS market has more than doubled in value over the years of 2005–2009 (Wierzejska *et al.,* 2014).

Chronic kidney disease (CKD) is a state of renal insufficiency with impaired excretion of numerous metabolites and waste products. Decreased urinary clearance of DS and their metabolites could be potentially harmful in patients with CKD. Taking into account the prevalence of CKD, estimated in Poland to be at 6% of the general population (Zdrojewski *et al.,* 2016), the issue of dietary supplementation in this patient group is of clinical importance.

The aims of the study presented here were to evaluate the prevalence of DS use in subjects with various forms and stages of CKD, to assess the major indications for DS consumption in CKD, and to obtain insight into the patients' knowledge and awareness concerning DS characteristics and potential side-effects.

## METHODS

A cross-sectional controlled survey study was conducted in CKD patients in order to evaluate the self-medication practice with DS. We primarily investigated the prevalence of DS use in CKD subjects, the types ofDS, as well as the major indications for their use.The classes of DS investigated were as follows: vitamins and minerals, omega-3 fatty acids, glucosamine, supplements for sexual potency, for weight loss, homeopathic agents, analgesics, herbs, and/or other. The study included 180 patients with CKD treated in the Department of Nephrology, Transplantology and Internal Medicine of the Medical University of Gdansk. CKD was diagnosed according to the KDOQI definition (National Kidney

**Table 1. Demographic dataof the study groups; CKD – chronic kidney disease, *versus* control group**

| | All CKD patients | Control group | p-value |
|---|---|---|---|
| Number of patients (n) | 180 | 60 | |
| Male gender (%) | 101 (56.1%) | 32 (53.3%) | NS |
| Age (years) | 58.0 ± 15.1 | 57.3 ± 14.3 | NS |
| | | | NS |
| Living conditions:<br>Good<br>Average<br>Poor | 62 (34.4%)<br>108 (60.0%)<br>10 (5.6%) | 24 (40.0%)<br>34 (56.7%)<br>2 (3.3%) | |
| | | | NS |
| Education:<br>Basic/Professional<br>Secondary<br>Higher | 22 (12.2%)<br>106 (58.9%)<br>52 (28.9%) | 8 (13.3%)<br>34 (56.7%)<br>19 (31.3%) | |
| | | | NS |
| Place of residence:<br>Big city > 100 000<br>Small city < 100 000<br>Village | 123 (68.3%)<br>36 (20.0%)<br>21 (11.7%) | 43 (71.7%)<br>12 (20.0%)<br>5 (8.3%) | |
| Co-morbidities:<br>Hypertension<br>Diabetes mellitus<br>Cardiovascular disease | 123 (68.3 %)<br>43 (23.9%)<br>24 (13.3 %) | 32 (53.3%)*<br>5 (8.3%)**<br>9 (15.0%) | <0.05<br><0.01<br>NS |

NS = non-significant

2002). Patients were divided into subgroups: CKD stage 1–5 (CKDND, n=80), end-stage renal failure patients treated with hemodialysis or peritoneal dialysis (CKDD, n=50), and subjects after kidney transplantation (CKDT, n=50). Glomerular filtration rate (GFR) was estimated based on the CKD-EPI equation (Levey *et al.,* 2009).

Sixty age-and gender-matched subjects without CKD serving as a control group were selected from the cohort of the Family Medicine Centre of the same hospital. The written anonymous survey consisted of 22 multiple-choice questions related to the respondents' demographic background, place of residence, level of education, living conditions, medical conditions and self-medication practices with DS. These included: the types of DS in use, frequency of DS use (never, sometimes, regularly i.e. >1 time/week), major indications, the source of DS (prescribed by the doctor, by the pharmacist, advised by massmedia, etc.), as well as the patient's awareness of the potential side-effects of the DS. Protocol of the study received approval from the Local BioethicsCommittee.

## Statistics

Results were expressed as percentages (for categorical variables), mean and standard deviation or median and interquartile range. The assumption of normality was verified with the Kolmogorov-Smirnov test. The quantitative variables' differences were assessed by *t*-test, analysis of variance (ANOVA) or non-parametric Kruskal-

**Table 2. Demographic data of the study subgroups:**
CKDND – non-dialysis dependent CKD patients (CKD stage 1–5); CKDD – dialysis subjects; CKDT – patients after kidney transplantation

| | CKDND | CKDD | CKDT | *p*-value |
|---|---|---|---|---|
| Number of patients (n) | 80 | 50 | 50 | |
| Age (years) | 64.2 ± 14.7 | 59.3 ± 14.0 | 50.1 ± 12.5 | <0.001 |
| Gender M: n (%) | 41 (51%) | 28 (56%) | 32 (64%) | 0.37 |
| Other diseases: n (%)<br>Diabetes mellitus<br>Hypertension<br>CVD | 29 (36)<br>56 (70)<br>14 (17) | 7 (14)<br>28 (56)<br>7 (14) | 7 (14)<br>39 (78)<br>3 (6) | 0.001<br>0.06<br>0.17 |
| Education: n (%)<br>Basic<br>Secondary<br>Higher | 7 (9)<br>45(56)<br>28(35) | 7 (14)<br>31(62)<br>12(24) | 8 (16)<br>31 (62)<br>11 (22) | 0.62<br>0.88<br>0.47 |
| Place of residence: n (%)<br>City > 100 000<br>City < 100 000<br>Village | <br>66 (82)<br>7 (9)<br>7 (9) | <br>38 (76)<br>10 (20)<br>2 (4) | <br>20 (40)<br>20 (40)<br>10 (20) | <br>0.001<br>0.001<br>0.16 |
| Living conditions: Good<br>Average<br>Poor | 22 (27)<br>55 (69)<br>3 (4) | 24 (48)<br>20 (40)<br>6 (12) | 16 (32)<br>33 (66)<br>1 (2) | 0.18<br>0.008<br>0.03 |

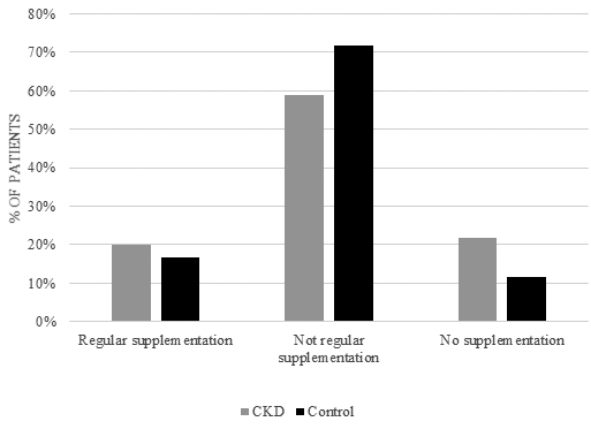


**Figure 1. Regular, irregular, or no use of DS among CKD patients and controls.**

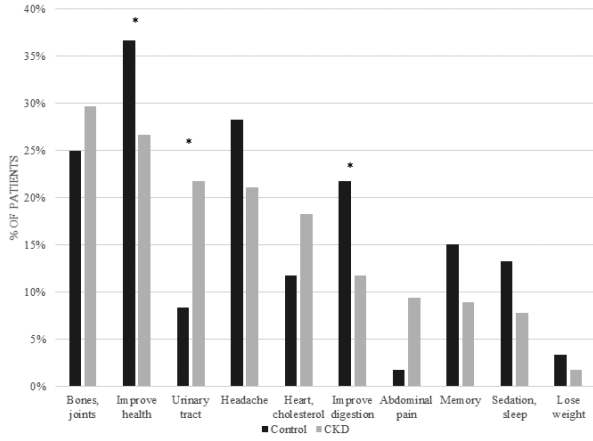


**Figure 3. Common conditions/diseases reported for DS use among CKD patients and controls.**

Wallis test. Differences in prevalence between selected categories were measured using the Chi ($\chi 2$) square test. A $p$-value $< 0.05$ was considered to be statistically significant. Statistical processing of the results was performed with the use of the statistical software STATISTICA PL v 12.0 (Statsoft, Kraków, Poland).

## RESULTS

The demographics of the studied groups are depicted in Table 1. Patients with CKD declared greater comorbidity, as compared to subjects from the control group. Subgroup analyses of CKD patients revealed that renal transplant recipients (CKDT) were younger and lived in less populated places than CKDND and CKDD patients (Table 2). There were also less diabetic subjects among the transplanted and dialysis patients, as compared to CKDND group.

The practice of DS use was found not to be significantly different between subjects with and without CKD (Fig. 1). Among patients with CKD, gender, age and place of residence were significantly associated with DS use. Women had higher DS use than men (89% *vs.* 70%; $p$=0.003), and DS was higher in older persons (mean age of patients regularly taking DS *vs.* those taking the mir regularly or never was 63.4 ± 13.5 *vs.* 57.8 ± 15.3, respectively; $p$=0.045) and in people living in cities in comparison to patients living in the countryside (81% *vs.* 63%; $p$=0.049).

In the CKD group, DS most commonly used were: minerals ubstances, vitamins, and herbs (Fig. 2). Major indications related to DS consumption reported by CKD patients were: musculoskeletal issues, general health improvement and prevention of urinary tract infections (Fig. 3). The decision to introduce DS was made by the patient's doctor in 54% of cases; by a pharmacist in 9% of cases, and by the patients themselves in 37% of cases. The results obtained in the control group did not differ significantly in this regard (50%, 13% and 37%,respectively).

The vast majority (84%) of patients with CKD declared that their doctor was informed about the DS used. In the control group, this percentage was lower (62%; $p$=0.001).

Only 21% of patients with CKD, and 27% of subjects without CKD declared knowledge of any possible side-effects associated with DS use (NS). Other patients stated that DS were completelysafe.

Subgroup analyses revealed that CKDD patients were characterized by a significantly higher DS use in comparison to CKDND and CKDT renal transplant recipients (Fig. 4). CKDD reported taking more vitamin sandl-carnitine than other CKD patients, while the use of omega-3 fatty acids was the most frequent in the CKDND group (Table 3). Although there were differences

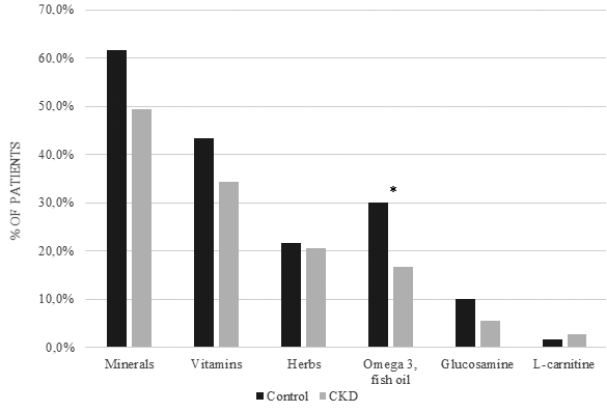


**Figure 2. The most common DS consumed by CKD patients and controls.**

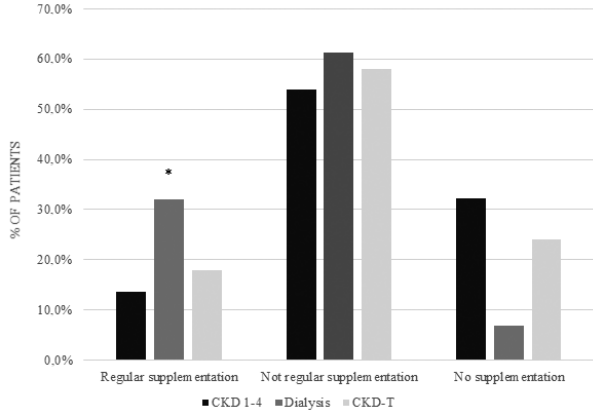


**Figure 4. DS use in CKD subgroups.**

**Table 3. The most common DS consumed by CKD subgroups;**
CKDND – non-dialysis dependent CKD patients (CKD stage 1–5); and CKDD – dialysis subjects; CKDT – patients after kidney transplantation

| | CKDND | CKDD | CKDT | *p*-value |
|---|---|---|---|---|
| Minerals | 47.5% | 56% | 46% | 0.544 |
| Vitamins | 23.7% | 46% | 40% | 0.021 |
| Herbs | 22.5% | 22% | 16% | 0.642 |
| Omega-3, fish oil | 25% | 6% | 14% | 0.015 |
| Glucosamine | 7.5% | 2% | 6% | 0.407 |
| L-Carnitine | 1.25% | 8% | 0% | 0.027 |

in the indication for DS use among the CKD subgroups, they reached a statistical significance only in the case of DS used for headache, as this indication was more prevalent in CKDD and CKDT patients, as compared to CKDND subjects (Table 4).

## DISCUSSION

The study presented here reveals that DS use is as prevalent in CKD patients as it is in the general population. This finding is of clinical significance because despite the wide spread consumption of DS, there is a lack of data on DS use among patients with CKD. In the few studies from various parts of the world completed up to date, the prevalence of DS use among CKD patients was similar to that found in the present evaluation (Kara, 2009; Nowack *et al.,* 2009, Tangkiatkumjai *et al.,* 2014). Analysis within the CKD population revealed that there are some differences among particular groups. The higher prevalence of vitamin use in dialysis patients might be explained by the more frequent use of vitamin D in this patient group, as compared to CKDND and renal transplant subjects. However, it has to be highlighted that the study presented here evaluated only the use of over-the-counter medications. In Poland, cholecalciferol belongs to this group, while most CKD patients take 1-hydroxy-cholecalciferol, which is sold on prescription only, and therefore has not been included in this analysis. The higher proportion of patients taking fish oil supplements in the CKDND cohort might derive from the belief of nephroprotective properties of this DS.

Intense advertising and over-the-counter availability results in consumption of DS that is growing worldwide, with vitamins and minerals commonly used to promote general health and decrease the risk of chronic diseases. This holds true despite the fact that the efficacy of DS is highly doubtful. There is no doubt that in specific cases of mineral and/or vitamin deficiencies, DS are indispensable. However, large, well-designed studies in the general population, as well as in various patient groups, consistently show no effect of DS use on mortality, cardiovascular disease, or cognitive function. High-dose oral multivitamin and multimineral regimen used as a secondary cardiovascular prevention in patients with a history of myocardial infarction did not reduce cardiovascular events in a statistically significant way (Lamas *et al.,* 2013). In a long-term, randomized, placebo-controlled trial among almost six thousand men aged 65 years or older, those assigned a daily multivitamin supplement had similar overall cognitive performanceas those receiving a placebo (Grodstein *et al.,* 2013). When evaluating the studies combined in the form of meta-analysis, there was no evidence of supplements affecting cardiovascular disease, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies(Fortmann *et al.,* 2013).

In CKD patients, DS are used for similar reasons as in the general population. The major indications include

**Table 4. Indications for DS use in the CKD subgroups;**
CKDND – non-dialysis dependent CKD patients (CKD stage 1–5); CKDD – dialysis subjects; and CKDT – patients after kidney transplantation

| | CKDND | CKDD | CKDT | p-value |
|---|---|---|---|---|
| Musculoskeletal | 35% | 30% | 20% | 0.19 |
| General health improvement | 20% | 38% | 26% | 0.77 |
| Urinary tract | 26% | 12% | 24% | 0.14 |
| Headaches | 12% | 30% | 26% | 0.04 |
| Cardiovascular system | 21% | 18% | 14% | 0.58 |
| Digestion | 10% | 12% | 14% | 0.78 |
| Abdominal pain relief | 9% | 10% | 10% | 0.96 |
| Memory improvement/preservation | 9% | 10% | 8% | 0.94 |
| Sedation/sleep facilitation | 6% | 6% | 12% | 0.42 |
| Weight reduction | 4% | 1% | 0% | 0.27 |

general health improvement and protection of bones and joints. As renalosteodystrophy is a common complication of CKD, this finding does not surprise. Our study reveals that the use of DS affecting the urinary tract is more prevalent in CKD subjects, in comparison to controls with no kidney disease. The major supplements reported by patients in this regard were various herbs for prevention of urinary tract infections, and for improvement of urination. For dialysis patients, dietary recommendations include supplementation of vitamins that are lost to dialysate during the treatment (Clase *et al.,* 2013). Calcium supplements are advised for prevention of renal osteodystrophy. Data from the literature also demonstrates more specific indications for DS in this patient population, as for instance fish oil supplementation and aspirin for arteriovenous fistula protection in patients requiring hemodialysis (Irish *et al.,* 2017) or alpha-tocopherol for prevention of cardio-vascular mortality in the highly burdened diabetic hemodialysis cohort (Espe *et al.,* 2013). Similarly to the results in the general population, these DS have not been found to be associated with clinical benefit in most studies (Espe *et al.,* 2013; Irish *et al.,* 2017), although there are reports on improvement in lipid profile, oxidative stress, pruritus or erythropoietin demand in CKD patients following intake of omega-3 polyunsaturated fatty acids (Vergili-Nelsen, 2003; Bouzidi *et al.,* 2010).

However, patients with CKD constitute a different population than people with no kidney disease. Impaired renal function can lead to accumulation of DS and/or their metabolites for which the urinary tract is the primary path of elimination. That is the case of magnesium. Mild hyper magnesaemia develops in most CKD patients when the glomerular filtration rate is less than 30 ml/minute, since magnesium excretion decreases even though fractional excretion of magnesium is increased (Felsenfeld *et al.,* 2015). Nevertheless, magnesium supplementation is highly prevalent in CKD subjects. It has to be acknowledged though, that increased magnesium concentration might be beneficial for CKD subjects, as it has been shown to inhibit phosphate-induced vascular calcification in experimental settings (Bressendorff *et al.,* 2017). Currently ongoing studies will probably reveal whether this favorable property is of clinical significance (Bressendorff *et al.,* 2017). Nevertheless, most of multimineral DS contain phosphates and numerous multivitamin DS contain potassium. The dangers associated with increased consumption of both in the CKD population are well acknowledged and obvious.

However, some of DS can, independently from renal function, be harmful to kidneys. Aristolochic acid, found in some herbal supplements, is an acknowledged cause of 'Chinese herbs' nephropathy and is involved in the pathomechanism of Balkan endemic nephropathy (Jadot *et al.,* 2017). Experimental data, as well as some clinical reports, point to the possibility of kidney injury caused by glucosamine through induction of apoptosis in the tubular and mesangial cells of the kidney (Gueye *et al.,* 2016). High vitamin E consumption leads to increased content of biomarkers of tissue toxicity and oxidative stress in the kidneys of mice (Jansen *et al.,* 2016). In general, DS containing aristolochic acid, glucosamine, potassium, and phosphates ought to be avoided in CKD patients. In renal transplant subjects, all DS that interfere with the cytochrome P450 pathways should not be used because of the risk of interactions with immunosuppressive medicines (Chen *et al.,* 2012). Comprehensive lists of potentially nephrotoxic DS are available online and in the literature (Brown, 2017).

The knowledge on the potential side-effects of dietary supplementation is scarce, both in the general population, as well as in CKD patients. Only 1/5 of the studied cohort of CKD subjects declared any awareness of any possible risks associated with DS use. The remaining 80% of patients stated that DS were completely safe. This finding underlines the importance of a meticulously elicited medical history of DS use, and enlightening the patients of the potential risks associated with dietary supplementation.

The major limitations of the study presented here include its cross-sectional character, and a relatively small sample size. The DS were classified arbitrarily, and some agents from one class of DS could be used for various reasons, as for instance vitamin C for urinary tract infection prevention. However, while formulating the questionnaire, the aim was to make it as easy and straightforward for the patient as possible. Nevertheless, it included 22 questions.

In conclusion, the prevalence of DS use is similarly high in the CKD patients as it is in people with preserved renal function, with the exception of those on dialysis. In addition, the pattern of DS use varies slightly with CKD subjects interested in improving urinary tract function. The patients' knowledge on the side-effects of DS is very limited. Taking into account the potential risks associated with the accumulation of DS in the course of CKD and/or the nephrotoxic potential of some DS, the necessity of a meticulous interview on DS use, and of comprehensive information provided to the patient, seems of crucial importance.

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