

Article

Efficacy of a Food Supplement Based on Collagen and Magnesium Combined with Pelvic Floor Muscle Training Exercises in Women with Urinary Incontinence: A Double-Blind, Randomized, Pilot Clinical Trial

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Abstract: Background/Objectives: Urinary incontinence (UI) is a common condition affecting women worldwide, with pelvic floor muscle training exercises (PFMT) recognized as the first-line treatment for UI. Supplementation with bioactive compounds, such as collagen and magnesium, may enhance the effectiveness of PFMT. This study aimed to evaluate the efficacy of combining a food supplement containing collagen and magnesium with PFMT in women experiencing stress (SUI), urge (UII), or mixed (MUI) urinary incontinence. Methods: A pilot clinical trial was carried out on 44 women with stress, urge, or mixed urinary incontinence. The improvement in urinary incontinence was assessed, before and after 6 weeks (W6) of product use, by the Questionnaire for Urinary Incontinence Diagnosis (QUID) and the clinical assessment of the gynecologist. Quality of life (QoL) was assessed as a secondary endpoint. Results: At Week 6, the baseline median QUID score in the active group was significantly reduced by 64% ($p < 0.001$), with 76% finishing the study with a negative diagnosis for UI. In contrast, the placebo group showed a reduction in QUID score by only 10% ($p < 0.001$), with just 25% of participants achieving a negative diagnosis for UI. QoL statistically significantly ($p < 0.001$) improved by 76% in the active group, while no changes were observed in the placebo group. Conclusions: Supplementation with the (Dermoxen[®] PelviPlus[™]/Dermoxen[®] Gynable[®] Urocollagen[™]) tested product significantly improved urinary symptoms and quality of life, demonstrating a greater effect than pelvic floor muscle training (PFMT) exercises alone. Dermoxen[®] PelviPlus[™]/Dermoxen[®] Gynable[®] Urocollagen[™] demonstrated efficacy across all three subtypes of UI.

Keywords: collagen; magnesium; supplementation; urinary incontinence; clinical trial

1. Introduction

Urinary incontinence (UI), defined as any “complaint of involuntary loss of urine” [1], is a widespread condition among women worldwide. The prevalence of UI rises with age and is reported to affect 58–84% of women, with most studies reporting a prevalence of any UI in the range of 25–45% [2–4]. The high variability in the reported prevalence of

UI can be attributed to cultural differences in the perception of UI, variations in study methodologies, and inconsistencies in its definition [3,5]. Despite its high prevalence, UI remains underdiagnosed since up to half of the affected women may refrain from reporting it to their healthcare provider due to embarrassment or the misconception that UI is a natural part of aging [6].

Incontinence types can be classified according to their pathophysiological mechanism as (a) stress urinary incontinence (SUI) when the urethral closure mechanism functioning is poor and the anatomic urethral support is lost, (b) urge urinary incontinence (UUI) when bladder detrusor muscle involuntary contracts during the filling phase of the micturition cycle, and (c) mixed urinary incontinence (MUI) when there is the concomitant presence of defective urethral closure or support mechanisms and of detrusor overactivity [6,7]. From a clinical perspective, SUI is defined as the complaint of involuntary urine leakage of urine during activities that increase abdominal pressure (such as exercise, sneezing, or coughing), UUI is defined as the complaint of involuntary urine leakage accompanied by or immediately preceded by a sudden, compelling urge to urinate that is difficult to postpone, while MUI is characterized by the presence of both SUI and UUI symptoms [8].

UI negatively affects the quality of life (QoL), affecting different areas of the subjects' life including, social, work, psychological, and sexual wellbeing [9,10]. A detrimental impact of UI has been observed on sexual function, affecting 26% of women with SUI and 43% of women with UUI [11]. The impact of UI QoL is not yet fully understood, highlighting the need for more comprehensive research and targeted investigation to fully capture its multifaceted consequences [10].

UI not only affects the QoL of the individual afflicted but is also a significant economic burden for healthcare services [12]. The annual cost of UI in Sweden, for example, has been reported to account for approximately 2% of the total healthcare budget [13]. Recent international research on the economic burden of urinary incontinence estimates that the cost of continence care in Europe will reach €69.1 billion in 2023. Without proactive measures to improve continence health, this financial burden is projected to increase by 25%, reaching €86.7 billion by 2030 [14–16]. Moreover, toileting assistance associated with UI imposes a significant substantial additional burden on family caregivers and nursing facilities staff [17–21].

Our pilot study aimed to assess the preliminary overall efficacy of a commercially available food supplement (Dermoxen[®] PelviPlus[™] or Dermoxen[®] Gynable[®] Urocollagen[™], Ekuberg Pharma, Carpignano Salentino, Italy) when used in conjunction with regular pelvic floor muscle exercises (PFMT) to improve the UI symptoms and the QoL in women with SUI, UUI, or MUI. The results of this study will be used to design a study with sufficient statistical power to assess the efficacy of the product within each UI sub-population. This food supplement was specifically formulated to support the pelvic floor with collagen and to help normal muscle functioning with magnesium. A study conducted by Gong et al. reported collagen abnormalities linked to an imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in women with weakened pelvic support tissues [22]. Similarly, research by Chen et al. reported a 60% reduction in total collagen content per milligram of protein in women with SUI compared to controls [23]. These findings suggest that SUI may be associated with increased MMP-mediated collagen degradation within the extracellular matrix of pelvic floor support tissues, resulting in insufficient support for the bladder neck and urethra [24,25]. Magnesium was demonstrated to be effective in improving detrusor instability or sensory urgency in women [26]. The food supplement also contained ingredients that have beneficial effects in preventing urinary tract infections (cranberries and horsetail extracts), in muscle strength

(Vitamin D), and in reducing the degradation of bladder structure due to lack of estrogens (*Cimicifuga racemosa* extract) [27–34].

2. Materials and Methods

2.1. Trial Design

This single-center randomized (1:1 ratio), double-blind, placebo-controlled pilot trial was conducted over a 6-week follow-up period at the Nutratch S.r.l. facilities (Rende, CS, Italy) between June and September 2024. It consisted of a screening visit, a baseline visit (W0), and a follow-up (W6) visit after 6 weeks of product use. Eligible subjects were enrolled at baseline by a board-certified gynecologist and randomized to receive the active or the placebo product. After the baseline visit, subjects received detailed instruction and training on pelvic floor muscle exercises from a physiotherapist (Figure S1).

The trial protocol (NT0000653/24 vers. 01 by 29 May 2024) was approved on 13 June 2024 (EC ref. no 2024/04) by an independent Ethics Committee (“Comitato Etico Indipendente per le Indagini Cliniche Non Farmacologiche”, Genova, Italy). The trial was registered on the ISRCTN registry (registration no. ISRCTN43204817). All study procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki. Participants were informed about the risks and benefits of the trial. Informed consent was obtained from all subjects involved in the study.

2.2. Participants

Eligible participants were healthy Caucasian women aged 45 to 70 years claiming stress and/or urge urinary incontinence (UI). Before inclusion in the trial, the diagnosis of stress or urge UI was confirmed by a board-certified gynecologist based on clinical anamnesis and the answers to the Questionnaire for Urinary Incontinence Diagnosis (QUID, Table S1). The cut-off value was set at ≥ 4 for SUI and ≥ 6 for UII [35]. Exclusion criteria included a positive medical history of pathologies (acute, chronic, or progressive) or pharmacological treatments (i.e., alpha-adrenergic blockers/stimulants, anticholinergics, calcium channel blockers, psychoactive drugs, misoprostol, opioids, hormone replacement therapy, diuretics) that could potentially interfere with the test product; simultaneous participation in other clinical trials; participation in a similar trial without an adequate washout period; food intolerance or food allergies (including allergies to ingredients of the test product); concomitant use of food supplements, topical products, or procedures to treat UI; prior use of UI-active products or procedures without an adequate washout period; history of drug, alcohol, or substance abuse; nutrition and eating disorders (bulimia, psychogenic eating disorders, etc.); pregnant or breastfeeding women; and absence of adequate contraceptive measures in women of childbearing age.

2.3. Intervention, Randomization, and Compliance with Treatment

After the enrolment, subjects were assigned to receive the active or the placebo products in a 1:1 ratio. The active arm (DXP) received (daily) 1 stick pack of a commercially available food supplement (Dermoxen[®] PelviPlus[™] or Dermoxen[®] Gynable[®] Urocollagen[™], Ekuberg Pharma, Carpignano Salentino, Italy) containing isomalt, *Actaea racemosa* L. rhizome dry extract (titrated to 2.5% saponins), vitamin D3 (100,000 IU/G cholecalciferol), tribasic magnesium citrate, hydrolyzed marine collagen, creatine monohydrate, *Equisetum arvense* L. herb dry extract (titrated to 2.0% in silica), *Vaccinium macrocarpon* Aiton fruit dry extract (titrated to 10.0% in proanthocyanidins), citric acid (E330), lemon flavoring, sucralose, and silicon dioxide. The placebo arm (PLA) received (daily) 1 stick pack having the same appearance as the active product and containing isomalt, citric acid, lemon flavoring, sucralose, and silicon dioxide.

The food supplement used in this clinical trial is the exclusive property of Ekuberg Pharma and is marketed worldwide under the tradenames Dermoxen® PelviPlus™ and Dermoxen® Gynable® Urocollagen™. A restricted randomization list was generated by PASS 11 (version 11.0.8, PASS, LLC, Kaysville, UT, USA) using the “Efron’s biased coin” algorithm. Participants received the food supplement in sealed boxes, each with a uniquely coded label to maintain blinding. The randomization list was securely stored in sealed, opaque envelopes numbered sequentially, ensuring that neither the investigator nor the participants were aware of the product assignment.

Participants were instructed to report the occurrence of adverse events throughout the study. Compliance with the treatment was determined by counting and recording the unused stick packs at the end of the 6-week treatment period, with a compliance threshold defined as $\geq 80\%$. Participants with compliance below 80% were excluded from the intention-to-treat (ITT) population due to poor adherence to the treatment regimen.

2.4. Primary and Secondary Endpoints

The primary efficacy endpoint was the improvement in UI symptoms from baseline to 6 weeks, as assessed by the QUID questionnaire and the gynecologist assessment. Additional analysis was performed on participants who demonstrated an improvement in their QUID scores. Any adverse event was also assessed as a primary outcome.

The secondary endpoints of the trial were assessing improvements in participants’ QoL and confirming product tolerability.

2.5. Outcomes

The Questionnaire for Urinary Incontinence Diagnosis (QUID) [35] was used to distinguish SUI and UI and to follow the improvement of UI symptoms over time. The QUID is a self-administered, 6-item questionnaire for UI symptoms, proven to be reliable and valid when compared to standard clinical evaluations in outpatient urogynecology settings [36]. The first three items of the questionnaire address symptoms of SUI, while the remaining three focus on UI symptoms (Table S1). Possible answers to each item are six frequency-based options (from “none of the time” to “all of the time”) scored on a 6-point scale (from 0 to 5). Scores are calculated additively, yielding separate Stress and Urge scores, each ranging from 0 to 15 points.

At the end of the treatment period, the gynecologist assessed the product’s efficacy using a verbal rating scale to address a question on treatment effectiveness (“Was the treatment effective?”). The scoring system was based on a verbal rating scale (VRS) as follows: 1. No, completely disagree, 2. No, disagree, 3. Yes, agree, and 4. Yes, completely agree.

The QoL questionnaire consisted of 10 items focused on the participant’s perception of the UI discomforts in the last two weeks (Table S2). Answers were on an 11-point numerical rating scale (NRS) from 0 (“not at all”) to 10 (“maximum discomfort”).

2.6. Statistics

As this research was conducted as a pilot trial primarily intended to provide preliminary efficacy data for the product, a formal sample size calculation was not performed.

Data normality was checked by the Shapiro–Wilk W test. Since all the data were not normally distributed, non-parametric tests were used. The Wilcoxon test was employed to evaluate intragroup differences compared to baseline, while the Mann–Whitney U test was used to assess intergroup variations between DXP and PLA at week 6 (W6). All statistical analyses were two-sided with a significance level set at 5% ($p < 0.05$) and were performed using Rstudio 2024 (version 2024.4.1.748; Posit Software, PBC, Boston, MA, USA). The output of statistical tests was reported as follows: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

3. Results

3.1. Subject Characteristics, Compliance with Treatment, and Tolerability

The study screened a total of 56 subjects ($n = 56$), with 12 excluded for the following reasons: 6 failed to meet the inclusion criteria, 5 declined participation, and 1 initiated pharmacological therapy. A total of 44 subjects ($n = 44$) with SUI, UII, or MUI were successfully randomized into two treatment groups (DXP or PLA), with 22 subjects in each group. A total of 41 subjects completed the study (per protocol population). One subject in the DXP group and two subjects in the PLA group withdrew from the study for personal reasons unrelated to product use. The participants' flow chart is presented in Figure 1.

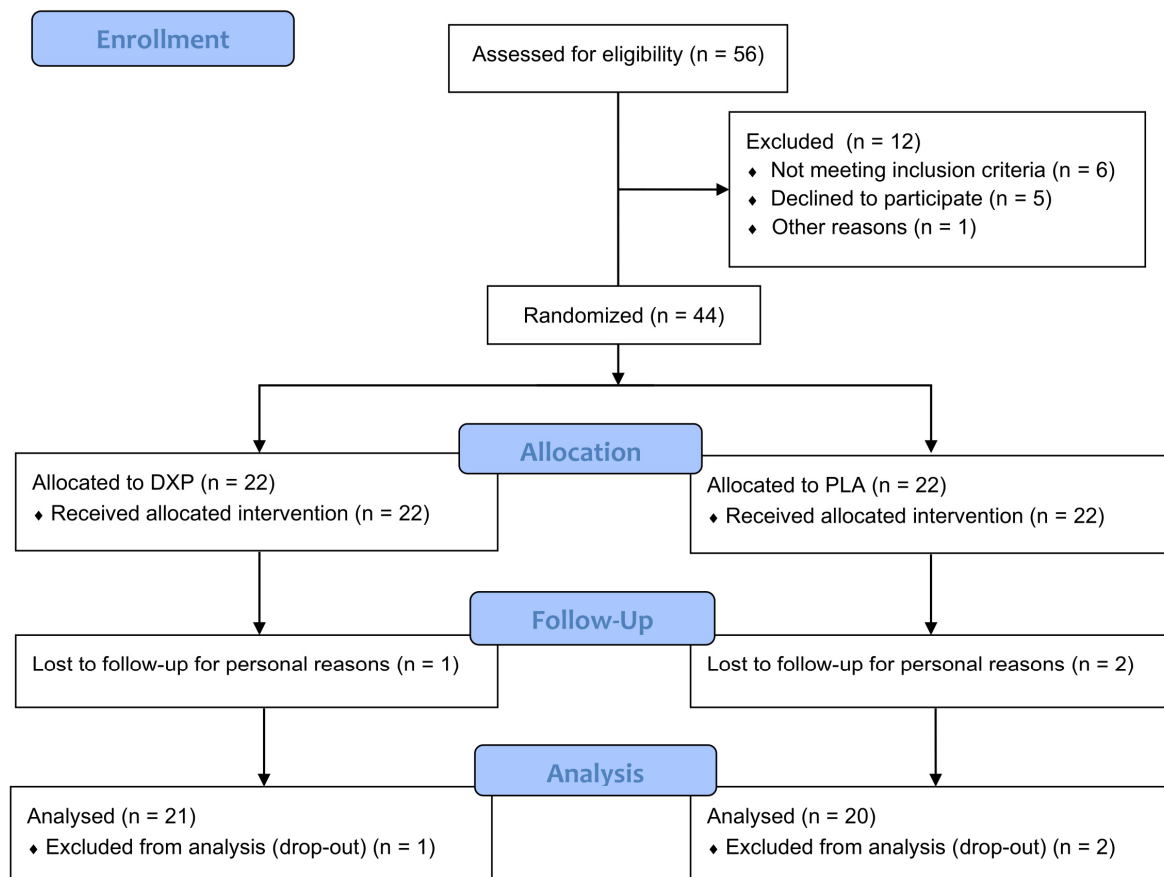


Figure 1. Participants' flow diagram.

The mean age was 58.6 ± 1.7 in the DXP group and 53.7 ± 1.3 in the PLA group. The distribution of subjects with SUI, UII, or MUI was balanced across the treatment groups. Additional demographic and baseline data are provided in Table 1.

Table 1. Baseline and demographic characteristics.

	DPX (n = 21)	PLA (n = 20)	p Value ¹
Age (years)	58.6 ± 1.7	53.7 ± 1.3	0.060036
UI diagnosis			
Stress (SUI)	7 (33%)	11 (52%)	n.a.
Urge (UII)	3 (14%)	1 (5%)	n.a.
Mixed (MUI)	11 (52%)	8 (38%)	n.a.
QUID score	11 (10–14)	10 (8–12)	0.079650

Continuous variables are presented as mean $\pm$ standard error, non-continuous variables as median (IQR), and categorical variables as counts and percentages (in brackets). ¹ Two-sided Mann–Whitney U test.

The compliance with treatment was above 95% for both groups (DPX = $97 \pm 1\%$, range 83–100%; PLA = $98 \pm 1\%$, range 90–100%).

3.2. Primary Outcomes

At baseline, the QUID total score was 11 (IQR 10–14) in the DPX group and 10 (IQR 8–12) in the PLA group. After 6 weeks of treatment, the QUID total score in the active group was statistically significant ($p < 0.001$), reduced by 64% (Figure 2a). In the placebo treatment arm, the QUID score showed a slight reduction of 10%, which was statistically significant ($p < 0.001$). The variation in QUID scores at week 6 (W6) between the DXP and PLA groups was statistically significant ($p < 0.001$). Interestingly, a reduction in the QUID score corresponded to a negative diagnosis of UI in 76% ($n = 16$) of DXP-treated subjects, compared to only 25% ($n = 5$) of PLA-treated subjects.

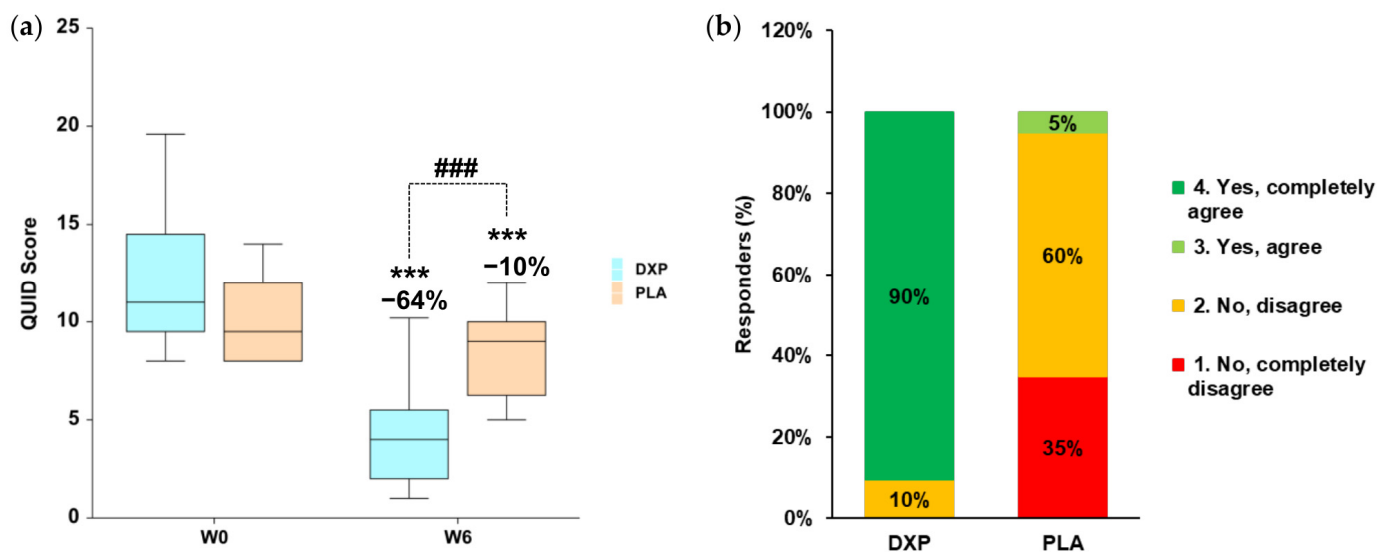


Figure 2. Primary outcomes. (a) QUID score. (b) Efficacy scoring by gynecologist. The intragroup (vs. baseline) statistical analysis is indicated by the symbol *, while the intergroup (DXP vs. PLA) statistical analysis is indicated by the symbol #, as follows: ***/### $p < 0.001$.

The efficacy of the DXP treatment was positively evaluated by the gynecologist in 90.5% of participants, compared to only 5% in the PLA group (Figure 2b). The global scoring between the DXP (median 4 “Yes, completely agree”; IQR 4–4) and the PLA (median 2 “No, disagree; IQR 1–2) treatment was statistically significant ($p < 0.001$).

3.3. Secondary Outcomes

After 6 weeks of treatment, the quality of life in the DXP group improved by 76% (Table 2), while no change was observed in the PLA group.

The improvement of QoL was associated with a reduction of the UI-related discomforts having a negative impact on the social functioning, the daily activities, and the mood of the affected subjects. In the PLA group, performing only PFMT exercises had no effect on QoL. At W6, the QoL scores for each item were statistically significantly different between the DXP and PLA treatment groups (Table 2).

Table 2. QoL questionnaire output. Data are median (IQR). DW6 is the percentage variation vs. baseline.

No.	Items	DXP			PLA			<i>p</i> value ¹
		W0	W6	DW6	W0	W6	DW6	
01	Physical activities	5 (4–7)	1 (1–3)	−80%	5 (4–6)	4 (3–5)	−20%	<0.001
02	Social activities	4 (3–6)	1 (0–3)	−75%	4 (3–6)	4 (3–5)	0%	<0.001
03	Relationships/interactions	4 (3–5)	1 (0–2)	−75%	4 (3–6)	4 (3–5)	0%	<0.001
04	Outdoor activities	4 (3–5)	1 (1–3)	−75%	5 (3–6)	4 (3–6)	−20%	<0.001
05	Activities at home	3 (2–5)	0 (0–1)	−100%	4 (2–4)	4 (2–4)	0%	<0.001
06	Productivity	4 (2–5)	1 (0–2)	−75%	4 (4–5)	4 (2–5)	0%	<0.001
07	Ability to travel	5 (4–6)	2 (1–3)	−60%	5 (3–6)	5 (3–6)	0%	<0.01
08	Feeling stressed	5 (3–6)	1 (1–2)	−80%	4 (4–5)	4 (2–5)	0%	<0.001
09	Feeling sad	4 (3–5)	1 (1–1)	−75%	4 (3–5)	4 (2–5)	0%	<0.001
10	Feeling embarrassed	5 (4–6)	1 (1–3)	−80%	5 (4–7)	5 (3–6)	0%	<0.001
Overall		45 (32–52)	11 (9–19)	−76%	43 (37–55)	42 (31–50)	−2%	<0.001

¹ Two-sided Mann–Whitney U test carried out on W6 DXP vs. W6 PLA.

4. Discussion

The economic burden of urinary incontinence on healthcare services and its impact on family caregivers have been increasing in recent years, a trend exacerbated by an aging society [14]. In the “integrated care for older people (ICOPE) guidelines”, the World Health Organization (WHO) identified urinary incontinence (UI) as a priority issue, recognizing its detrimental effects on the quality of life of older adults, their overall health status, levels of depression, and need for care [37]. Non-pharmacological treatments are the most effective and safe approach to reduce the economic burden of urinary incontinence (UI) on healthcare systems, particularly in low- and middle-income countries, while also minimizing the risk of caregiver strain and burden [37,38].

Pelvic floor muscle training (PFMT), first described by the American gynecologist Kegel, is the first-line treatment for UI [39]. However, several studies have reported that the efficacy of intensive and frequent PFMT practice supervised by qualified personnel rates from 29% to 59% and lasting for at least 3 months, as recommended by the European Association of Urology (EAU) [40–43]. A systematic review by Riemsma et al. also found that the percentage of responders to PFMT varies depending on the subtype of UI, with SUI subjects showing the highest response rate (58.8% of responders) and UUI subjects the lowest (17% of responders) after 12 months of supervised PFMT [40].

In the scientific literature, there is increasing evidence of the role of food supplements in maintaining general health and in reducing the risk factor for a disease [44]. However, the number of studies evaluating the relationship between food supplements, PFMT, and improvements in urinary incontinence (UI) is limited [45]. To address this gap, we decided to explore the impact of food supplementation combined with pelvic floor muscle training (PFMT) exercises on managing urinary incontinence (UI) symptoms. The key ingredients of the tested food supplement included collagen, aimed at counteracting the natural collagen degradation associated with aging, and magnesium, intended to alleviate detrusor instability and sensory urgency [22–26]. The product formula also incorporated ingredients with beneficial effects on urinary and pelvic health, including cranberries and horsetail extracts for preventing urinary tract infections, Vitamin D for muscle strengthening, and *Cimicifuga racemosa* extract to mitigate bladder structure degradation associated with estrogen deficiency.

Our findings clearly demonstrated the efficacy of food supplementation in increasing the percentage of responders (i.e., subjects with a negative diagnosis for UI) to PFMT

exercises from 25% to 76% and in reducing UI-related discomforts. Interestingly, the rate of improvement of PFMT exercises that we observed is comparable with the rate of improvement reported in the literature [42,43]. The active product also proved to be effective in improving quality of life (QoL), demonstrating a significant reduction in discomforts related to social functioning (−75%), daily activities at home (−100%) and outdoors (−75%), as well as mood disturbances (−75%) of the affected subjects. This positive effect is an important step toward fostering age-friendly conditions (alignment of life span with health span) that promote the independence of elderly individuals, helping them maintain autonomy and avoid feeling like a burden to society.

The strength of this study is its study design (randomized clinical trial), the blind allocation to treatments, the high compliance with treatment (>95%), and the positive results obtained in only 6 weeks. Despite these strengths, this study has some limitations. The study population enrolled subjects claiming UI without specific repartition by subtypes. Combined with the relatively small sample size, this limitation prevents a robust subanalysis of the results for each UI subtype. In this regard, the data obtained from this study, including the variability of the preliminary endpoint and its standard deviation, will be used for sample size calculation for future studies. The reliance on a validated questionnaire alone for urinary incontinence assessment, without the inclusion of urodynamic testing or a pad test, was a weakness of the trial. Another limitation was the lack of a post-treatment follow-up period, which prevented the assessment of the product's effects after discontinuation. Finally, our trial does not provide a clear understanding of the supplement's mechanism of action. Future studies with a larger sample size are needed to explore these aspects in greater detail.

5. Conclusions

Our results clearly demonstrate the efficacy of oral supplementation with collagen and magnesium combined with PFMT in improving the UI-associated discomforts and the quality of life of the affected subjects.

The putative mechanism of action underlying our results may involve a positive effect on the pelvic floor muscles, enhanced support for the pelvic floor tissues, and improved regulation of detrusor instability or sensory urgency.

Based on our findings, we can conclude that daily supplementation with Dermoxen® PelviPlus™ or Dermoxen® Gynable® Urocollagen™ combined with pelvic floor strengthening can be a successful strategy for better urinary control after only 6 weeks of treatment.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/uro5020007/s1>, Figure S1: Instructions for performing Kegel exercises to strengthen pelvic floor muscles; Table S1: Template for the Questionnaire on Urinary Incontinence Diagnosis (QUID); Table S2: Template for the Quality of Life (QoL) Questionnaire.

Author Contributions: Conceptualization, V.N., C.S., E.D.C. and D.C.; methodology, F.A. and E.D.; validation, V.N., R.V. and M.M.; formal analysis, R.V., E.D. and V.N.; investigation, M.M.; resources, D.C. and F.A.; data curation, R.V. and V.N.; writing—original draft preparation, V.N.; writing—review and editing, V.N.; visualization, V.N.; supervision, F.A.; project administration, F.A.; funding acquisition, G.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the independent Ethics Committee ("Comitato Etico Indipendente per le Indagini Cliniche Non Farmacologiche", Genova, Italy) on 13 June 2024 (EC ref. no. 2024/04).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. However, the data are not publicly available as they are the property of the study sponsor (EKUBERG pharma s.u.r.l., Carpignano Salentino, Italy).

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Conflicts of Interest: D.C., C.S. and E.D.C. are employed full-time at Ekuberg Pharma. The other authors declare no conflicts of interest. The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

UI	Urinary incontinence
PFMT	Pelvic floor muscle training
SUI	Stress urinary incontinence
UUI	Urge urinary incontinence
MUI	Mixed urinary incontinence
QUID	Questionnaire for urinary incontinence diagnosis
DPX	Active product
PLA	Placebo product
QoL	Quality of life
MMP	Matrix metalloproteinases
TIMP	Tissue inhibitors of metalloproteinases
VRS	Verbal rating scale
NRS	Numerical rating scale
ICOPE	Integrated care for older people
WHO	World health organization
EAU	European association of Urology
EC	Ethical committee

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