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Original Article

Systematic review and meta-analysis of the effectiveness of urea-based moisturizer on dry skin in diabetes melitus patients with parameters stratum corneum hydration and xerosis assessment scale

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Abstract

Background Diabetic patients have dry skin which tends to progress to diabetic feet, secondary infections to amputations which can reduce the patient's quality of life. The high prevalence of diabetes in Indonesia causes diabetic ulcers and ends in amputation. In Indonesia, the amputation rate is still high, which is around 25%. Moisturizer is used as a daily treatment for dry skin in diabetic patients. Therefore, moisturizers are needed as a preventive and treatment step to prevent these complications. Based on available scientific data, urea is the gold standard in the treatment of dry skin. This is based on various studies that report that most show, urea is superior to other moisturizers to restore skin hydration.

Methods Searching the electronic information service Pubmed-MEDLINE, Scopus, EBSCO, ProQuest, Scopus, Cochrane library, ClinicalTrials.gov, and Google Scholar, discovered 6 articles were considered in the qualitative analysis The meta-analysis includes 5 publications (n=331 subjects) and 371 subjects (n=371 participants).

Results The findings of a meta-analysis revealed that after the treatment of urea-based moisturizer, the SCH values after urea administration was higher than the control and XAS scores after urea administration was lower than the control. The mean difference of the total standardized in SCH values between subjects receiving urea compared to those receiving control was 0.493±0.186 (95% CI, 0.129 to 0.857). These findings show that the group receiving topical urea had considerably higher in the total of SCH levels than the control group. (P=0.008). The total standardized mean XAS score difference between participants receiving Urea and those receiving controls was -2.184±0.140 (95% CI, -2.458 to -1.909.) These results indicate the overall XAS score the group receiving topical urea was substantially lower than the comparison group overall (P=0.000).

Conclusion Based on data from a systematic review and meta-analysis, it could be inferred that urea-based moisturizer administration is superior to other control in improving dry skin hydration in diabetic patients.

Key words
Diabetic skin, xerosis, skin hydration.

Introduction

Dry skin in patients with Diabetes Mellitus (DM) is a skin condition due to reduced moisture in the stratum corneum (SC) caused by a state of hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action or both, causing the skin become rough, scaly,

peeling, thickened, fissures and itching.[1,2] Hyperglycemia causes an imbalance of natural moisturizer factor (NMF) and intercellular lipids, inhibits keratinocyte proliferation and migration, decreases epidermal turn over, increases transepidermal water loss (TEWL), advanced glycation end products concentration in serum. (AGEs), decreased expression of aquaporin-3 (AQP-3), and autonomic neuropathy resulting in disruption of skin barrier homeostasis.[3-5] According to research by Pavlovic *et al.* dry skin is one of the most common skin conditions in DM patients.[6]

Diabetes mellitus causes various complications such as dry skin which tends to become diabetic ulcers and ends with amputation so that it can reduce the patient's quality of life. The prevalence of DM in Indonesia increased in 2007 was 1.1% while in 2013 it was 2.1%.[7,8] Dry skin conditions in DM patients have a prevalence of more than 40% and are found in 1 of 4 DM patients. Research by Galdeano *et al.* in Argentina stated that 69% of DM patients had dry skin.[9] A descriptive study in Pekalongan, Central Java stated that 65.7% of DM patients had dry skin.[10] Dry skin in DM patients had the most severe impact, namely amputation. where in Indonesia, the amputation rate is around 25% so that it pays special attention.[1,11]

The National Institute for Clinical Excellence (NICE) guidelines show that one of the effective foot care in DM is using moisturizer as a preventive measure. For this reason, using moisturizers as an ongoing daily treatment is recommended by international guidelines. The amputation rate due to dry skin leading to the formation of fissures and ulcers in DM can be decreased by 60-70% with proper chiropody in DM patients.[12] Moisturizers that can be used for dry skin in DM patients are humectants, emollients and occlusives.[13]

Urea is a humectant, based on its effectiveness, it is the most preferred choice as a moisturizer for dry skin in DM patients. Urea has an advantage over other types of moisturizers is that it has a low molecular mass of 200-300 Da (500 Da), allowing it to penetrate the epidermal layer of skin and reach the more profound layers. For application, urea easily absorbs into the skin.[2,14] Other moisturizers such as glycerin, lactic acid are also preferred humectants because of their effectiveness, but according to some studies urea is superior.[15] Occlusive such as petrolatum have limitations because of their oily texture and stickiness to clothes, making them less desirable, smelly and can cause potential allergens.[16] The use of urea in combination with other additives gives more significant results on dry skin in DM patients. Urea in combination with other humectants, emollients or occlusives is used to enhance hydration.[17,18]

Assessment of dry skin in DM patients can be done using the Xerosis Assessment Scale (XAS) and stratum corneum hydration (SCH) parameters as measured by corneometry. Clinically dry skin can be assessed using the XAS scores on a nine-point scale (0-8). A decreased XAS scores indicates improved skin hydration. Corneometry evaluates the water content of SK expressed in arbitrary units (AU). An increased SCH values indicates an improvement in skin hydration.[16,19] Three studies on topical urea on dry skin of DM patients with XAS parameters reported that urea moisturizer could significantly reduce XAS scores in the experimental group against control.[18,20,21] Two studies on topical urea on dry skin of DM patients with SCH parameters

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reported that urea moisturizer could significantly increase the SCH value in the treatment group compared to the control group.[17,22]

Material and Methods

Data was collected through the use of online databases such as Scopus, Pubmed-Medline, ClinicalTrials.gov, Ebscohost, Scopus, Cochrane library, ProQuest, and Google Scholarbesides manual searching from Indonesian libraries from 2012 to 2021 was also carried out. This study is classified as an observational meta-analysis, a systematic review, and a meta-analysis. This study's population was the product of clinical studieson the urea-based moisturizer application on dry skin of DM patients.

This study's sample is a scientific article on Inclusion criteria include: Research using topical urea 5-10% with additives for dry skin in patients with diabetic, randomized clinical trials, subjects who has moderately severe dry skin, subjects not used moisturizers or keratolytics in the last 2 weeks, subjects used urea moisturizer for 2-4 weeks, subjects not to take drugs that can cause dry skin (vitamin A derivatives, statins, chemotherapy, diuretics) and hyperkeratotic states that are not associated with any metabolic diseases (ichthyosis, atopic dermatitis, psoriasis), research outcomes are XAS scores and SCH values. Exclusion requirements studies included case reports, serial cases, letters, and literature reviews published in neither Indonesian nor English.

Research Procedures

Data source and online database search strategies involvethe databases Medline Pubmed, EBSCOhost, Scopus, ProQuest, ScienceDirect, SpringerLink, Elsevier Clinical Key, Cochrane library, ClinicalTrials.gov. Other references include library database, conference papers, fieldwork researchers, and publications. The data sources examination was conducted until the data was analysed.

To establish three subcategories of citations, the following Medical Subject Headings (MeSH) phrases were employed (1) urea; (2) skin; (3) diabetes mellitus. To generate a subset of citations relevant to the study issue, the three subgroups were merged using the Boolean operators 'AND'. The PRISMA flowchart from 2009 was employed to conduct the literature review. Three researchers performed an independent literature review to determine citation lists of all major papers and the most updated literature review was performed to detect missing publications. Consensus was used to settle any differences in article selection and data extraction.

Data were extracted separately by three researchers using the provided data extraction forms. Both intervention and without intervention of urea, moisturizers, as well as XAS scores and SCH scores were documented. The Cochrane Risk of Bias Tool for Randomized Controlled Trials was used to examine the risk of bias.

Data analysis

Regarding the data processing, the data collection was reviewed for reliability and consistency. The data will then be entered into the computer. Both intervention and without intervention of urea, moisturizers, as well as XAS scores and SCH scores were retrieved and entered into the form of data extraction.

Comprehensive Meta-Analysis: A software application for Meta-Analysis, Version 3.3 was used to examine the systematic review and meta-analysis of mean differences between the experimental and comparison groups.

Result and Discussion

Comprehensive Meta-Analysis: A software application for Meta-Analysis, Version 3.3 was used to examine the systematic review and meta-analysis of mean differences between the experimental and comparison groups.

Data searches were carried out online at Pubmed-MEDLINE, Scopus, EBSCO, ProQuest, Scopus, Cochrane library, ClinicalTrials.gov, and Google Scholar, along with manual search from Indonesian libraries with a time range till the study was completed. The scavenge found 132 publications. After examining the title and eliminating any duplicates, we got 24 relevant article titles. After reviewing the abstracts of these publications, 18 articles were eliminated including 13 primary research articles outside the topic of this meta-analysis, 3 titles without complete papers, 1 clinical article title and 1 other title being an observational study. Six complete papers were evaluated for acceptability and utilized in qualitative and quantitative research to assess the effectiveness of topical urea as a moisturizer on dry skin of DM patients.[17,18,20-23]

Research Characteristics

Descriptive analysis of research characteristics consisted of the country of implementation, research design, number of samples, research subjects, age range, gender of the subject, type of DM, and length of treatment. The majority of research sites were carried out in France (n=4), followed by England (n=1), Italy (n=1) and Greece (n=1) in the period 2008-2017. Four studies used an RCT design, 2 clinical trials and 1 single blind controlled pilot study. The total sample of 7 studies is 397 people. The seven studies selected foot xerosis in DM patients as research subjects. Seven studies took samples of the total gender, namely 183 male samples and 214 female samples. The seven studies took samples of DM type, namely DM type 1 as many as 67 people and DM type 2 as many as 330 people. Two studies have an age range of 40-75 years, the participants in one research ranged in age from 20 to 50 years.

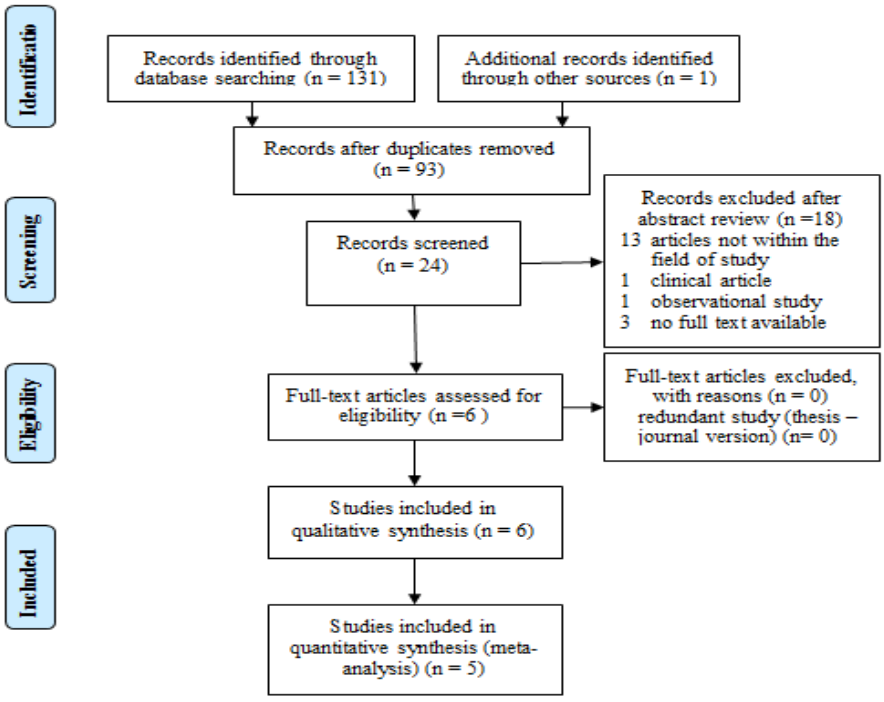


Figure 1 Flowchart of identification and selection of research literature in systematic review and meta-analysis.

Another research has an age span of 40-74 years and 3 studies have almost the same age range, namely 18-70, 18-75 and 18-80 year. Two studies assessed the use of topical urea compared to placebo controls.[20,21] Two studies compared urea with other moisturizers namely glycerin 40% and glycerin 15% plus vaseline 8%.[18,23] Two studies used a control by not moisturizing the other side of the foot.[17,22] The use of topical urea, placebo or other moisturizers was mentioned twice daily. Duration of treatment in 5 studies is 4 weeks, and 2 studies is 2 weeks.

Result of Qualitative Data Analysis (Systematic Review)

1. Garrigue et al. 2011 [20]

This research was carried out on 24 men and 30 women with type 1 or 2 DM patients with mild cases of dry feet to more serious one, who hadn't applied any moisturizer for at least 2 weeks before the study, comparing the use of a moisturizer containing 5% urea, 10% glycerin, 1% lactic acid, 8% paraffin with placebo, twice daily for 4 weeks. The selection of research subjects into the treatment group was done by randomization. Methods of randomization, blinding and allocation concealment were not mentioned in the journal. The age of the research subjects was 57.0±12.7 years. The duration of type 1 DM was 28.4±14.1 years and the duration of type 2 DM was 13.8±9.2 years. The standard treatment for all study subjects was that the patient was asked to apply a test cream and a placebo to his/her own right/ left leg at random. Before applying the patient washes his feet with soap and dried. The test cream or placebo is applied all over the feet to the sock area and massaged for 15 seconds. The subjects were instructed to clean their hands before applying the cream to the other leg. On the day of outcome measurement, the patient did not apply the test cream or placebo. The outcomes assessed in the study were XAS and overall clinical cutaneous score (OCCS), SCH, and scale measurements. Overall clinical cutaneous score is a measurement with a score of 15 points which is calculated by adding the XAS scores, skin roughness and hyperkeratosis assessment. Scale measurements were carried out using a D-Squame analysis tool in the form of a computerized image with parameters such as heterogeneousness, density, transmission density, and epidermal surface scale The mean XAS scores before and after treatment on the legs decreased by 4.2±1.3 and 1.7 in the urea group and 4.3±1.3 and 2.8 in the comparison groups. At 4 weeks after treatment there was a decrease of 61.9% in the urea group and 34.95 in the placebo group (P<0.0001). The SCH values before and after treatment on the legs increased by 48.90% and 57.30% in the urea group and 31.70% and 36.50% in the placebo group. SCH values increased significantly by 57.3% in the urea group and 36.7% in the placebo group (P<0.0001). The mean OCCS values before and after treatment on the feet decreased by 6.0±1.9 and 2.2 in the urea moisturizer group and 6.0±1.9 and 3.8 in the placebo group. The mean value of both groups decreased significantly by 63.3% in the urea group and 36.7% in the placebo group (P<0.0001). Scale measurement values using the D-squame tool before and after treatment, it was only the scale of density and index of heterogeneity which improved considerably in the urea group compared to placebo.

2. Gin et al. 2017 [21]

This research was carried out on 167 study subjects with type 1 or 2 DM patients with foot xerosis with deep open fissures, comparing the use of moisturizers containing 5% urea, 10% glycerin, 1% lactic acid, 8% paraffin (n=80) with placebo. (n=87) with a frequency of twice a

day for 4 weeks. The selection of research subjects into the treatment group was done by randomization. Randomization was done with 4 computerized blocks. On the first day, the researcher allocated the research cream number to each subject based on the sequential sequence of appearance on the same day. Both researchers and the treatment was concealed from the research subjects. The median age of study subjects was 63.6 (54.8-70.4) years. The median duration of DM was 7.3 (3.6-13.8) years with type 1 DM being 3.6% and type 2 DM being 96.7%. The standard treatment for all study subjects was that patients did not use any moisturizer for 2 weeks before treatment. The urea group and the placebo group applied to both feet after previously being washed and dried. The cream is applied thinly on the entire foot including the heel and lateral then massaged until fully absorbed. The outcomes assessed in this study were XAS, medical score of the examiner for fissure closure, and overall assessment of fissure healing. The primary variable is the ultimate repair of the crack on the foot's heel which consists of a 3 point scale, namely assessing the healing of the fissure, closed superficial fissure or open deep fissure. Second variable involved the comprehensive crack repair, fissure closure, and complete fissure healing in both legs after 2 and 4 weeks. A clinical assessment of overall fissure healing has a scale of 1 to 5; scale 1 shows significant increase and 5 shows regression. The mean XAS for improvement of foot xerosis decreased at the end of the study in both the urea and placebo groups. The mean XAS scores before and after treatment on the legs were 3.4 and 1.0 in the urea group and 3.6 and 1.9 in the placebo group. The change in mean value from guideline was quantitatively substantially larger after 4 weeks of therapy in the urea group [-0.93, standard error (SE) (0.20)] compared to placebo [-1.11 (0.19)] with a mean difference between the two groups of -0.82 (CI 95%, -3.4 to -0.31; P=0.002). The percentage of study subjects (95%CI) with a target fissure healed after 4 weeks was 46.5% (35.7% to 51.7%) in the urea group and 33.3% (24.3% to 43.8%) in the placebo group. the difference between groups was not statistically significant (P=0.088). The RR for therapeutic effect (95% CI) was 1.93 (0.95 to 2.03). There was no substantial intervention by gender, according to post-hoc analysis. The percentage of study subjects who still showed an open deep fissure following 4 weeks of therapy was found to be 4 times lower in the urea group (6.4%) than comparison group (P=0.002). A post-hoc investigation revealed that the difference between the groups was quantitatively meaningful (P=0.002) and RR for therapeutic effect (95%CI) 0.27 (0.10 to 0.67). Overall adherence was less in the urea group compared to the control was less in the urea group compared to the control (75.7% and 90.1%).

3. Seite et al. 2011 **[**17]

This study was conducted on 40 people, 18 male and 22 female study subjects with type 1 or 2 DM under normal conditions, comparing the use of moisturizers containing 5% urea with other moisturizers (glycerin, sodium lactate, shea butter) with controlled controls. No treatment was given with a frequency of twice a day for 4 weeks. Methods of randomization, blinding and allocation concealment were not mentioned in the journal. The age of the research participants was 39±8 years. The time span of DM was 18±12 years with 32 people with type 1 DM and 8 people with type 2 DM. The standard treatment for all study subjects was that patients were asked to apply urea cream on one arm and one leg for 1 month. And the side of the arm/ leg next to it was a control that was not given any treatment. The findings evaluated in this research were SCH, desquamation index, TEWL, elasticity, and autofluorescence or

accumulation of AGEs. This assessment uses a non-invasive device. The mean values of SCH in the arms before and after treatment were 23.0±6.3 and 38.5±11.3 in the urea group and 22.7±1.1 and 26.6±1.4 in the comparison group (P<0.05). This result was increased in the urea group than the comparison group. The average value of SCH in the legs before treatment was 24±6, but the results after treatment in the urea and control groups were not included. In contrast, healthy control subjects (n=47, ages 20-50) had an average SCH values of 37±7 AU, 38 percent greater than DM participants in this research. The mean desquamation index values before and after treatment on the arm were 4.3±0.7 and 2.1±0.5 in the urea group and 4.5±0.7 and 4.7±0.7 in the control group (P<0.05). The mean TEWL values before and after treatment on the arm were 4.3±0.7 and 2.1±0.5 in the urea group and 4.5±0.7 and 4.7±0.7 in the control group. These results showed a lower value in the urea group compared to the controls (P<0.05). The mean values of skin elasticity before and after treatment on the arm were 0.60±0.2 and 0.81±0.6 in the urea group and 0.74±0.7 and 0.70±0.3 in the control group (P<0.03). The mean values of autofluorescence before and after treatment on the arm were 2.12±0.5 and 2.27±0.5 in the urea group and 2.14±0.5 and 2.23±0.5 in the control group (P<0.06).

4. Federici et al. 2015 **[**18]

This fact-finding study was arranged on 50 study subjects with DM who had moderate to severe foot xerosis, comparing the use of moisturizers containing 5% urea, 0.4% arginine, 0.01% carnosine (n=25) with 40% glycerin moisturizer (n=25) with the frequency of administration twice a day for 4, 12 and 32 weeks. The selection of research subjects into the treatment group was done by randomization. Randomization was carried out with an allocation ratio of 1:1 using 4 computerized blocks. The research participants' age range was 62±9 years in the urea group and 62±9 in the glycerin. The duration of DM in the urea group was 12±6 years and in the glycerin group it was 11±6 years. All study subjects were patients with type 2 diabetes. The standard treatment for all study subjects was not to use any moisturizer 2 weeks before the study. Both research groups applied moisturizer to the feet, namely dorsal and plantar areas, as well as the distal part of the legs. The amount of 2.5 grams of cream is applied per application. Patient compliance is seen from the use of the product in the container given every time it arrives. Prior to skin analysis measurements, subjects were asked to be in a room with a temperature of 20ºC±2º and 50% humidity for 30 minutes. Outcomes assessed in this study were XAS and overall cutaneous score (OCS) as primary outcomes and skin hydration and desquamation as secondary outcomes. Overall cutaneous score has a 3-point scale, namely 0=normal skin, 2=mild hyperkeratosis, 3=severe hyperkeratosis. Semiquantitative skin analysis reads a scale for water content in the skin using a score of 1 extremely lack of moisture) to 10 super moisture skin) with a score of 5-6 being typical skin. The score for cell desquamation uses a point scale of -5 (soft skin) to +5 (very damaged skin) with a score between -1 to +1 for normal skin. Baseline values in both urea and glycerin groups were overall balanced. The mean XAS scores before and after treatment on the legs were 5.5±1.1 and 3.9 for the urea group and 5.3±0.9 and 5.0 for the glycerin group. The XAS rates in the urea group was considerably lower over 4 weeks compared to the glycerin group. (P=0.0014). OCS values decreased by 27% from the beginning to the end of this research, while they elevated by 8% in the glycerin group (P=0.02; between the two groups). The mean values of skin hydration and desquamation before and after 32 weeks in the water content assessment were 2.9±1.4 and

5.1±0.9 in the urea group (P=0.001) and 28±1.0 in the glycerin group. The desquamation or cell scores were 2.6±2.3 and 0.6±0.9 in the urea group and 2.2±1.0 in the glycerin group.

5. Papanas et al. 2011 **[22]**

This research was performed on20 research subjects with type 2 diabetes mellitus, comparing the use of moisturizers containing 10% urea with the contralateral side control, not given treatment by giving twice a day for 2 weeks. The methods of randomization, blinding and concealment of allocations were not mentioned in the journal. The age of the research subjects was 61.40±2.44 years. The time span of DM was 8.20±2.55 years. All study subjects were people suffering from diabetes of type 2. The standard treatment for all research subjects was the application of urea to the plantar right foot, and there was no treatment on the left foot. At the time of examination, it will be read by 3 people and the value will be used for analysis. The examination was carried out in a room with a room temperature of 25ºC and sufficient humidity. The patient rests for a 10 minute acclimatization period before removing socks and shoes. The examination was carried out in the morning and the patient did not apply the urea solution that day. The result assessed was SCH. SCH values before and before treatment on the right leg were 26.55±4.14 and 32.5±4.54 in the urea group and 26.7±3.95 and 26.75±3.91 in the control group. The SCH value in the urea group considerably increased (P<0.001). SCH values in the left leg control group did not differ between baseline and 2 weeks after treatment (P=0.748).

6. Federici 2012 **[23]**

This study was conducted on 40 research subjects with type 2 diabetes with moderate to severe foot xerosis, comparing the use of a 5% urea moisturizer containing 0.4% arginine, 0.01% carnosine (UC) (n=20) with glycerin, vaseline, and paraffin cream (EC) with a frequency of twice a day for 4 weeks. The age of the research subjects was 66±7 years in the UC group and 58±8 in the EC group. The duration of DM was 14±6 years in the UC group and 9±3 in the UC group. All study subjects were patients with type 2 diabetes. The standard treatment for all study subjects was that both test and control groups applied moisturizer to the dorsal, plantar and distal third of the foot. Research subjects did not use any moisturizer 2 weeks before the study. Outcomes assessed in this study were Dryness Area Severity Index (DASI) and Visual Analoque Score (VAS). This score rates dry skin on a 5-point scale (0= not dry to 4= severely dry). The VAS scores assesses dry skin subjectively on a scale of 0= very dry skin and 10= very hydrated skin. The mean DASI values before and after treatment on the legs were 1.7±0.8 and 0.2 in the UC group and 1.9±0.5 and 1.0 in the EC group. In the mean of DASI, compared to the control group, the UC group performed much worse (P=0.048). Mean VAS values before and after treatment on the legs were 6.1±1.4 and 9.8 in the UC group and 7.3±1.2 and 8.2 in the EC group. The mean VAS in the UC group was substantially greater than in the controls (P=0.05).

Qauntitative data result (Meta-analysis)

Meta-analysis result effect of topical urea on SCH values

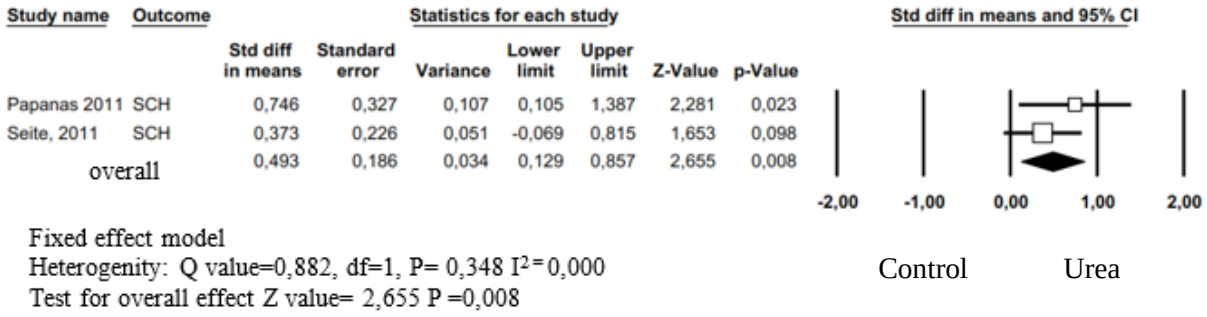
The mean score difference of SCH pre- and post- therapy in the intervention group who got topical Urea and the control is presented in **Table 1**.

In **Table 1** the difference in the value of SCH before before in the study of the topical urea group and the control group the value was

Table 1 Mean score difference of SCH values in the topical urea group compared to controls.

No	*Name of Researchers*	*Control type*	*Treatment*		*Control*	
			Average±SD	*n*	*Average±SD*	*n*
1	Papanas 2011	untreated	5.9±8.89	20	0.05±6.79	20
2	Seite 2011	untreated	15.5±44.01	40	3.9±0.54	40

Table 2 The meta-analysis results of the topical urea effectiveness on the SCH value in dry skin of DM patients.



positive. This indicates an increase in the SCH values after applying urea topically. The research of Papanas *et al.* 2011 showed that the SCH values after urea administration, which was 5.9±8.89, was higher than the control that was not given moisturizer, which was 0.05±6.79. In the study of Seite *et al.* 2011 showed the value of SCH after administration of urea, 15.5±44.01 higher than the control without moisturizer, 3.9±0.54.

In **Table 2** the findings of a meta-analysis on the efficacy of topical Urea on SCH values in dry skin of DM patients. The The heterogeneity result demonstrates Q's value=0.882 df=1 P=0.348 I2=0.000. This indicates that the data are homogenous, as indicated by the statistical Q test and heterogeneity results, the I2 test outcomes are not significant, indicating that the data are homogeneous. Since this data were homogenous, the analysis was conducted using a fixed effect model. The meta-analysis findings found that the statistical Q value of Z value=2.655 (P = 0.008). This demonstrates that the entire application of topical can drastically increase the SCH values on dry skin in DM patients.

The meta-analysis findings as a whole uncovered the fact that the total of standardized mean difference in SCH values between subjects receiving urea compared to those receiving control was 0.493±0.186 (95% CI, 0.129 to 0.857). These findings imply that the total SCH values of the group receiving topical urea was substantially higher than the controls as a whole (P=0.008).

Meta-analysis result effect of topical urea on XAS scores

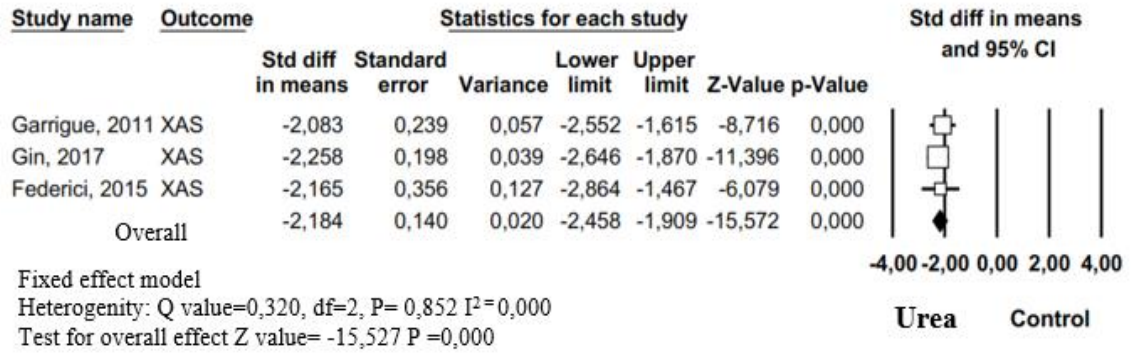
The mean score difference of XAS scores before and after treatment in the treatment group who received topical Urea and the control group is shown in **Table 3**.

In **Table 3**, the mean difference in XAS scores pre and post treatment in the topical urea group was negative. This indicates a decrease in XAS scores in dry skin of DM patients after therapy with topical urea. Moreover, the comparison group presented that the average difference in XAS scores after giving control was all negative. This shows that there was also a lowering XAS score in the control group following the treatment. Research by Garrigue *et al.* 2011 showed the XAS score after urea

Table 3 Mean score difference of XAS scores in the topical urea group compared to controls.

No	*Name of Researchers*	*Type of Control*	*Treatment*		*Control*	
			Average±SD	*n*	*Average±SD*	*n*
1	Garrigue 2011	Pacebo	-2.5±0.48	25	-1.5±0.48	25
2	Gin 2017	Placebo	-2.4±0.31	54	-1.7±0.31	54
3	Federici 2015	Gliserin 40%	-1.6±0.58	80	-0.3±0.62	87

Table 4. The results of the meta-analysis of the effectiveness of topical urea on the value of SCH in dry skin of DM patients.



administration, i.e. -2.5±0.48 showed a decrease compared to the control, namely, -1.5±0.48. In the study of Gin *et al.* 2017 Indicated that the XAS scores after urea administration was -2.4±0.31 also decreased compared to the control, which was -1.7±0.31. The research of Federici *et al.* 2015 showed that the XAS scores also decreased after urea administration, -1.6±0.58, lower than the control using 40% glycerin, which was -0.3±0.62.

In **Table 4** shows the meta-analysis findings evaluated the topical Urea efficacy on XAS scores on dry skin of DM patients. The heterogeneity test findings revealed the Q value=0.320 df=2 P=0.852 I2=0.000. This indicates that the data are homogenous, as indicated by the statistical Q test and heterogeneity results, the I2 test findings are not significant, indicating that the data are homogeneous. Since the data were homogenous, the assessment was performed using a Fixed Effect Model (FEM The meta-analysis findings revealed that the statistical Q value was z value=-15,572 (p=0.000). This implies that total topical urea treatment can dramatically lower the XAS scores in dry skin of DM patients.

The meta-analysis findings as a whole demonstrate that the total systematized mean difference in XAS scores between subjects receiving Urea compared to those receiving controls is -2.184±0.140 (95% CI, -2.458 to -1.909.) These results indicate the overall XAS scores. The group receiving topical urea was considerably decreased in comparison to the control group overall (P=0.000).

Assessment of publication bias can only be done if the entire publications used in the meta-analysis is more than 2 publications. Based on the above analysis, the existence of publication bias is carried out based on the XAS parameters. Egger regression test results obtained P value=0.717. This indicates that there is without bias in the publication.

The bias possibility of studies involved

There were five studies involved in the

Table 5 Risk of bias in studies used for systematic reviews and meta-analyses.

	Random Sequence Generation	*Allocation Concealment*	*Selective Reporting*	*Other Bias*	*Blinding of Parpicipants and Personnel*	*Blinding of Outcome Assesment*	*Incomplete Outcome Data*	*Standard AHRQ*
Garrigue dkk, 2011	?	?	−	+	+	+	+	*Fair*
Gin dkk, 2017	+	+	+	+	+	+	+	*Good*
Seite dkk, 2011	?	?	−	+	−	−	+	*Poor*
Federici dkk, 2015	+	+	+	+	−	+	+	*Fair*
Papanas dkk, 2011	−	−	+	+	−	−	+	*Poor*
Federici dkk, 2012	+	+	+	+	−	+	+	*Fair*

Circle symbol of ● with a positive sign indicating a low risk of bias, circle symbol of ● with a question mark the risk of bias cannot be assessed, circle symbol of ● with a negative sign indicates a high risk of bias.

meta-analysis, namely Garrigue *et al.* 2011; Gin *et al.* 2017; Seite *et al.* 2011; Federici *et al.* 2015 and Papanas *et al.* 2011 with data in the form of mean pre and post treatment. Research by Garrigue *et al.* 2011, Gin *et al.* 2017 and Federici *et al.* 2015 reported data with an XAS outcome. The studies of Seite *et al.* 2011 and Papanas *et al.* 2011 reported data with SCH outcomes. One other study had a different outcome, namely Federici *et al.* 2012 which reported DASI and VAS outcomes, so they did not belong to the quantitative analysis. The bias potential from included analysis research, both descriptive and analytical analysis, was evaluated using the Cochrane Risk of Bias Tool for Randomized Controlled Trials, including incomplete outcome data, blinding of outcomes, randomization, blinding of study subjects, allocation concealment, selection of reported outcomes, and also other biases. Each of these factors of the possibility of bias evaluation is then adjusted in accordance with Agency for Healthcare Research and Quality (AHRQ) criteria. **Table 5** presents the bias possibility evaluation.

Research by Garrigue *et al.* 2011 has strong possibility of biasfor selective reporting. In the study of Seite *et al.* 2011 experienced a strong possibility of bias in the critical report, blinding subjects and blinding outcomes. Research by Federici *et al.* 2015 and Federici *et al.* 2012 has a strong possibility of bias in blinding participants. In the study of Papanas *et al.* 2011 had a high risk of bias in the way of randomization, allocation concealment, blinding subjects and blinding outcomes. In the study of Gin *et al.* 2017 all assessment categories had a small possibility of bias. Two studies, namely Seite *et al.* 2011 and Papanas *et al.* 2011 are categorized as low quality of evidence. The research of Garrigue *et al.* 2011, Federici *et al.* 2017 and Federici *et al.* 2012 is categorized as moderate quality of evidence. Research by Gin *et al.* 2017 is categorized as good quality of evidence.

Discussion

This study is a systematic review, meta-analytic observational study, and meta-analysis on the

effectiveness of topical urea as a moisturizer on dry skin of DM patients with SCH and XAS parameters. The value of SCH after the use of topical urea in the articles used showed an increase. This increase was significant in the research of Garrigue *et al*. 2011; Seite *et al*, 2011 and Papanas *et al*, 2011. This is in accordance with the hypothesis that topical application of urea to dry skin of DM patients can increase skin hydration. Urea as a moisturizer on dry skin of DM patients is a physiological humectant, namely NMF, which can replace urea in dry skin. The advantage of urea over other humectants is that it has a low molecular mass which is 200-300 Da (≤500 Da) so that it has the ability to permeate the skin's surface and reach deeper layers of the SK.[2,14] Urea is a natural hydrating substance found in human skin. The particle is a strong moisturizer and can also function as a peeling agent, increasing the efficacy of this chemical especially for dry skin conditions DM namely hyperkeratosis, fissures, and scaly.[20]

In other studies, such as Grether-Beck *et al*, demonstrated that urea is not only an emollient agent but also responsible for the increase cell differentiation, raise the level of expressiveness aquaporin genes, filaggrin, and transglutaminase, loricrin, thereby increasing keratinocyte differentiation. The increase in aquaporin synthesis in keratinocytes caused by urea might be as a critical component which further improves skin moisture.[24]

The value of SCH on a placebo such as the study of Garrigue *et al* also increased. However, the increase was only half of the SCH value in the urea group.[20] In the study of Seite *et al.* 2011 the value of SCH in the control group that was not given treatment only increased slightly but not significantly. This might be related to the moisturizing influence of the excipients in the placebo, which is widely recognized and regularly reported in the research of[17] Another moisturizing SCH value, namely aqueous cream as a control study, Papanas *et al.* 2011 showed no significant improvement. significant.[22]

The findings of a meta-analysis on the efficacy of topical Ureaon SCH values in dry skin of DM patients. The heterogeneity test showed the value of Q=0.882 df=1 P=0.348 I2 = 0.000. This demonstrates that the data are identical, as indicated by the statistical Q test and heterogeneity results, are not significant, indicating that the data are identical. Since the data were identical, the analysis was conducted using a fixed effect model. The meta-analysis study found that the statistical Q value was Z value=2.655 (P=0.008). This indicates that the total amount of topical urea administered can greatly increase the SCH values on dry skin in DM patients.

According to the findings of meta-analysis, the total standardized mean difference in SCH values between subjects receiving urea compared to those receiving control was 0.493±0.186 (95% CI, 0.129 to 0.857). The findings imply that the total of SCH score of the receiving topical urea group was substantially higher than the control as a whole (P=0.008).

XAS scores after the use of topical urea in the articles used showed an increase. This increase was significant in the research of Garrigue *et al*. 2011; Gin *et al*, 2011 and Federici *et al*, 2011. This is in accordance with the hypothesis that topical application of urea to dry skin of DM patients can reduce XAS scores. Xerosis assessment scale is a score used to clinically assess skin hydration. This scale analyses the number and size of skin flakes, scales and fissures on the skin with a score of 0-8, whereas a decrease in the XAS scores indicates clinically improved skin hydration.[16]

In a study reported by Pierard *et al*, it was shown that dry skin manifestations of DM were dehydration skin or xeroderma, and acquired ichthyosis, mainly involving the shins and feet.[25] In a latest study of 750 diabetic individuals, Demirseren *et al* discovered that the most prevalent skin manifestations were epidermis infections (47.5 percent), xeroderma (26.4 percent), and skin infections, inflammation (20.7%).[18]

The National Institute for Clinical Excellence (NICE) guidelines show that effective foot care in DM, one of which is the use of moisturizers as a precautionary measure. For this reason, the use of moisturizers as an ongoing daily treatment is recommended by international guidelines. According to research Augustin *et al*, Based on available scientific data, urea is the gold standard in the treatment of dry skin. This is based on various studies that report that most of them show, urea is superior to other moisturizers in the treatment of dry skin. Not only does urea effectively hydrate the skin, it also enhances the skin barrier function as well as a defense mechanism and hydration of the skin itself. The amputation rate due to dry skin leading to the formation of fissures and ulcers in DM is possible to minimize it by 60-70 percent with proper podiatry in DM patients.[2,12,18]

The meta-analysis findings evaluated the topical Urea efficacy on XAS scores on dry skin of DM patients. The heterogeneity test findings revealed the value of Q=0.320 df=2 P=0.852 I2= 0.000. This demonstrates that the data are identical, as indicated by the statistical Q test and heterogeneity results are not significant, indicating that the data are identical. Since the data were identical, the analysis was performed using a fixed effect model. The meta-analysis findings found that the numerical Q value was z value=-15,572 (p=0.000). This indicates that the cumulative of topical urea treatment could dramatically lower the XAS score in DM patients with xeroderma.

The results of the meta-analysis as a whole show that the difference in the total standardized mean in XAS scores between subjects receiving Urea compared to those receiving controls is -2.184±0.140 (95% CI, -2.458 to -1.909.) These results indicate the overall XAS scores. The group receiving topical urea was considerably decreased in comparison to the control group overall (P=0.000).

In addition to these parameters, there are several other parameters that have been reported in several of these studies. Other parameters are overall clinical cutaneous score (OCCS), scale measurement using the D-Squame® analysis tool, investigator's clinical score for fissure closure, and overall assessment of fissure healing, desquamation index, TEWL, elasticity, and autofluorescence or accumulation of AGEs, overall cutaneous score (OCS) as the primary outcome and skin hydration and desquamation, Dryness Area Severity Index (DASI) and Visual Analoque Score (VAS).

In the 2011 study, Garrigue *et al*. measured scale using the D-Squame® analysis tool. The D-Squame® analyzer is a tool that shows a computerized image with parameters such as heterogeneity, density, optical density, and surface area on a scale. One month after treatment, there were significant results, only the scale density and heterogeneity index considerably enhanced in the urea group compared to placebo. This is understandable due to the short duration of the study so that a longer duration of use is required for overall clinical improvement.[20]

Research by Seite *et al.* 2011 in addition to SCH parameters, also reported results with parameters TEWL, desquamation index, skin elasticity, and

autofluorescence or accumulation of AGEs. Using urea for 1 month induced an increase in Skin moisture was related to a considerable decrease in the desquamation index and TEWL. The stratum corneum is the outermost layer of skin that protects the body from external agents and controls exchange with the environment, especially TEWL. The structural shape of SK and the presence of a hygroscopic molecule, namely NMF, allows SK to retain water, thereby keeping the epidermis moist and elastic. Natural moisturizing factor has an important role in skin hydration in SK. The use of urea has proven to have significantly increased skin hydration.[2,17,25]

Parameters of skin elasticity the study of Seite *et al*. 2011 reported that people experienced type II diabetes showed less skin flexibility than those with type I diabetes, and the value of accumulation of AGEs was higher than people suffer from type I diabetes. According to the literature, preclinical and clinical research conducted over the last decade have demonstrated participation AGEs are strong against complications that occur, especially in type 2 diabetes. Reactive oxygen species (ROS) not only participate in the formation of AGEs, but also interfere the effect of AGEs on tissues concerned. The correlation between clinical problems of diabetes mellitus and oxidative stress derived from the metabolic disorder's production of large dosages of AGEs.[26]

Several clinical assessment parameters on dry skin such as DASI, VAS and OCS overall showed significant improvement. According to the literature, the turn over for the SK layer takes 13-14 days, while the total turnover time for the entire epidermal layer is 26-27 days. The moisturizer used takes 2 weeks to 1 month to give results on the skin, so that within 1 month of research clinical improvement can be seen, but longer research still needs to be done for clinical overall improvement of the skin.[2,13]

Conclusion

Based on the findings of a systematic review and meta-analysis, it is possible to infer that topical urea administration is superior to other moisturizers in improving hydration of dry skin in DM patients.

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