Does Zinc Supplementation Accelerate Wound Closure (Healing) Compared to Placebo in Injured Patients?

**Background and Rationale (Justification)**

The body undergoes significant physiological responses following an injury or any form of physical trauma. Body injuries may either be accidental or intentional, for example, in the case of surgery. Regardless, every type of wound healing is complicated and involves several stages. Wound healing is considered a physiological response to injury that is important in all kinds of tissue systems (Lin et al., 2017). Wound care is among one of the public health concerns, for example, Nussbaum et al. (2018) as cited by Lin et al. (2017) states that an economic evaluation conducted in 2014 on Medicare expenses related to wound care revealed that the annual costs for all types of wounds was between $28.1 and 96.8 billion. Further, Lin et al. (2017) indicate that the aging population and increased cases of diseases, such as obesity and diabetes, worsen the challenges inherent in wound treatment. The complex processes involved in wound healing include the repair of membranes, coagulation, inflammation control, angiogenesis, cell proliferation, remodeling of tissues, and the formation of scars (Lin et al., 2017). These functions are at the core of tissue architecture restoration. Therefore, significant research is being conducted to establish better approaches to wound treatment.

Good nutrition is not only important as a source of energy, but also provides the necessary building blocks for replacing the wound tissue. Unless the healing cells receive the appropriate nutrients, the implementation of the best wound care practices will not promote healing (Mackay & Miller, 2003). Nutritional factors impact a wide range of health conditions; for example, diabetes and heart failure and receiving an optimum degree of nutrition, maintain an individual's overall health (Bishop, Witts, & Martin, 2018). Regardless, health care professionals often do not appreciate the association between nutrition and wound healing. Attention is most of the time not given to such patients until the wound is infected or does not health at the expected time (Bishop et al., 2018). Zinc is involved in several complex processes in wound healing (Bishop et al., 2018; Mackay & Miller, 2003). In the inflammatory stage, zinc modulates immune response (Demling, 2009) with chronic zinc deficiency, according to Bonaventura, Benedetti, Albarède, & Miossec (2015), promotes inflammation. After an injury, the levels of zinc in healthy tissues are redistributed to the wounded area and improves the immune functioning, which promotes wound healing (Bishop et al., 2018). Therefore, zinc supplementation is considered effective in the promotion of wound healing for injured patients (Bishop et al., 2018). However, it is the role of any registered nurse engaged in wound care to provide care plans and recommendations that are based on evidence (Ubbink, Brölmann, Go, & Vermeulen, 2015). Therefore, this critical review of literature investigates the hypothesis that zinc supplementation accelerates wound closure (healing) among injured patients. An evaluation of the quality and validity of the findings' methodology and identify and existing gaps for future research is done.

**Systematic Critical Review of Research**

A systematic literature review of randomised control trials was done to identify the sources to be reviewed. An eligibility criterion was determined before the search that ensured that the PICOT question, as provided in the study's title, is comprehensively answered. Randomised Control Trials (RCTs) offer Level I evidence while attempting to establish the most effective treatment approach (Spieth et al., 2016). However, there is still a need to evaluate the methodological quality and the validity of the studies, as bias in the analysis may be present. The evaluation will be done using the modified Cochrane risk of bias tool for Interventional studies (Jargensen et al., 2016). The tool allows the identification of the risk of bias that negatively affects the internal validity of the findings, and is a reflection of the intervention's actual efficacy (Higgins et al., 2011). It uses a domain approach that allows the transparent judgment of the findings, a judgment table, and a narrative evidence description to judge each domain on the risk bias table. The risks are classified into three categories that are low risk, high risk, or unclear risk. The domains include selection, performance, detection, attrition, and reporting biases.

*Table 1:* Characteristics of the selected studies

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| **Authors Names** | **Publication Year** | **Design** | **Participants** | **Interventions & Comparator** | **Sample Size** | **Study Duration** | **Outcomes** |
| Ågren et al. | 2006 | Randomised, double-blind, placebo-controlled multicenter trial. | 64 patients  Aged 17–60 years. | Intervention.  3% zinc oxide.  Comparator.  Placebo. | N=33  N=31 | 54 days - 3% zinc oxide.  62 days - Placebo. | Topical zinc oxide increased (p < 0.001) wound ﬂuid zinc levels to 1,540 (1,035–2,265) µM and decreased (p < 0.05) the occurrence of *Staphylococcus aureus* in wounds.  Fewer zinc oxide (n=3) than placebo-treated patients (n=12) were prescribed postoperative antibiotics (p=0.005).  Serum-zinc levels increased (p< 0.001) postoperatively in both groups, but did not differ significantly between the two groups on day 7. |
| (Berger, Baines, Raffoul, & Benathan) | 2007 | A prospective, randomised, placebo-controlled trial. | 21patients.  Aged 35±11years.  Burns on 45±16% of their body surface area. | Intervention.  Intravenous copper, selenium, and zinc  Comparator.  Vehicle (V group) was given a saline solution.  Phenylalanine plus 6-[2H2] glucose and [2H5] glycerol. | N/A | 20 days | The patients’ mean age and burn severity did not differ significantly between the groups, nor between the skin investigations subgroups.  Plasma TE concentrations were significantly higher in the TE group.  In the burned areas, the skin contents of selenium (P=0.02) and Zinc (P=0.03) increased by day 20.  The supernatant to-plasma 13C enrichment ratio in burned skin was 0.363±0.094 (TE group) and 0.286±0.130 (V group) after 1h (NS) and 0.592± 0.153 (TE group) and 0.262±0.171 (V group) after 6 hours, which reflected lower catabolism in the TE group (P=0.03).  No significant differences in whole-body substrate turnover were found between the groups. |
| (Momen‐Heravi et al.) | 2017 | A randomised, double-blind, placebo-controlled trial. | 60 patients (aged 40–85 years old) with grade 3 diabetic foot ulcers. | Intervention.  220 mg zinc sulphate supplements containing 50 mg elemental zinc.  Comparator.  Placebo. | N=30  N=28 | 12 weeks. | Zinc supplementation was associated with significant reductions in ulcer length (-1.5±0.7 vs. -0.9±1.2 cm, p=0.02) and width (-1.4±0.8 vs. -0.81±1.0 cm, p=0.02).  In addition, changes in fasting plasma glucose (-40.5±71.0 vs. -3.9±48.5 mg/dl, p=0.02), serum insulin concentration (-8.0±15.4 vs. +1.1±10.3 mIU/ml, p=0.009), homeostasis model of assessment-estimated insulin resistance (-3.9±7.1 vs. +0.8±5.9, p=0.007), the quantitative insulin sensitivity check index (+0.01±0.03 vs. -0.002±0.02, p=0.04) and HbA1c (-0.5±0.8 vs. -0.1±0.5%, p=0.01) in the supplemented group were significantly different from the changes in these indicators in the placebo group. |
| (Strömberg & Ågren) | 1984 | A randomised, double-blind study. | 37 geriatric patients. | Intervention.  Gauze compress medicated with zinc oxide (400 µg ZnO/cm2).  Comparator.  Gauze compress without zinc oxide. | N =18 – Zinc oxide.  N=19 – No zinc oxide. | 8 weeks | The zinc-treated patients (83% success rate) responded significantly better (P<0.05) than the placebo-treated patients (42% success rate). |

*Table 2:* The assessment of the risk of bias

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| --- | --- | --- | --- | --- |
| **Study**  **Domain** | Ågren et al..  (2006) | Berger et al.  (2007) | Momen-Heravi et al.  (2017) | Strömberg & Ågren,  (1984) |
| Random sequence generation adequate? |  | ? |  | ? |
| Allocation concealment adequate? |  |  |  | ? |
| Blinding of participants adequate? |  |  |  | ? |
| Blinding of personnel adequate? |  |  |  | ? |
| Blinding of outcome assessors adequate? |  | ? | ? | ? |
| Was incomplete outcome data addressed? | ? | ? |  |  |
| Was it free of selective reporting? |  | x |  | x |



**Quality Assessment**

Randomisation allows participants to be equally placed in either the control or intervention groups. This makes the differences in the findings to be due to the intervention rather than the patient characteristics. Therefore, an adequate degree of randomisation decreases bias in the results. In the study by Ågren et al. (2006), there is a low risk of selection bias as the participants were allocated to each group using a computer-generated approach. Computer randomisation is a secure method that is considered secure for producing the same number of participants. Further, they used block sizes of four or six stratiﬁed for centre that allowed equal placement of participants in each group, hence the methodology's strength. The study was a double-blind study; hence both the staff and participants were blinded to the treatment codes.

Allocation involved the use of centrally packaged, consecutively numbered, identical packages containing zinc oxide/placebo meshes (Ågren et al., 2006). The investigators were required to select the next available number when a new patient came into the trial. The codes were kept confidential until the final assessments and conclusions drawn. Therefore, there was a low risk of performance bias. Independent individuals performed the analysis. The approach used to blind the investigators is indicated, hence highlighting a minimal risk of directional bias. At the start of the study, there were 64 participants, but later they noted that three of the patients dropped out for unknown reasons. However, it is not indicated how they analyzed the intention to drop out; hence there is an unclear risk of bias. In regards to selective reporting (SR), the study has a low risk of reporting bias. The checking of the trial registry number, "ISRCTN35311675” via www.controlledtrials.com website, indicated no differences in reporting.

In the study by Berger et al. (2007), there was a moderate risk of selection bias, as the selection of participants was done based on a developed inclusion and exclusion criteria, and hospital patient records. There was no mention of the series of randomisation used. A stratified approach to randomisation was used, and this was admitted within 6h of injury for individuals aged between 16 and 65 years and had burns that covered >20% BSA and 10% BSA assessed as surgical on admission, including healthy patients undergoing plastic surgery. In regards to allocation bias, there was low risk as a third party was used for randomisation and kept the data. Concerning the blinding of participants and staff, the same amount of zinc supplements and the placebo was given; hence they were both unaware of the interventions used hence low risk of performance bias. There was no indication of whether the assessors were blinded hence a high risk of detection bias. Therefore, there might be an under or overestimation of the degree of impact, an exaggeration of the odds ratios, and the outcomes measurements may be affected. In regards to incomplete outcome data, the study began with 21 patients where 12 patients underwent skin biopsies with only 10 patients completing the isotopic study, but they give the reason why the rest did not complete. The study did not mention how it dealt with those that did not complete the isotopy; hence the risk to attrition bias is not clear. For SR, the study does not provide a registration number; therefore, a high risk of SR bias.

The third study by Momen-Heravi, Barahimi, Razzaghi, Bahmani, Gilasi, & Asemi (2017) has a low risk of selection bias as the randomisation assignment was achieved via computer-generated random numbers. Further, randomisation was done as blindness by trained staff at the clinic that strengthened the methodology. The use of blindness by trained clinical staff also ensured a low risk in allocation bias. Also, the zinc and placebo capsules were the same in shape and size and manufactured by the same company. Moreover, it was a double-blind study; therefore, both participants and staff were blinded to the codes. The similarity in the zinc and placebo capsules ensured the participants and staff did not know what they were taking and giving, respectively. Therefore, there was low risk in the performance bias. The analysis was done independently, but the approach for blinding the assessors is not mentioned, hence having an unclear detection bias.

Further, 2 patients dropped out for personal reasons. The researchers provided highlighted a methodology that would deal with the drop put outcomes that is the Last-Observation Carried-Forward method (LOCF), which is based on the intention-to-treat (ITT) principle that reduced the possibility of attrition bias hence the study had a low risk of attrition bias. Also, conditions of health maintenance such as nutritional intake and physical activity were spelled out for all the participants, which further reduced attrition bias. Moreover, in regards to SR, the study provides a trial registry number, "IRCT201506215623N46," which, when searched online, revealed no differences in the results in the trail and the originally intended outcomes. Therefore, there is a low risk of SR bias.

In the final study by Strömberg & Ågren (1984), there was an unknown risk of selection bias because the study does not mention how the randomisation of participants was achieved. In relation to allocation concealment, there was also an unknown risk of bias as there is no mention of who bore the responsibility of allocating the participants into the different groups and providing the supplement and placebo. This is assumed inferentially based on the fact that is a double-blind study. However, the double-blind nature ensured that a low risk of performance bias as both the participants and staff did not know what they were administering. Also, the approaches used for blinding are not mentioned in the study; hence there is an unclear detection bias. Further, no patient dropped out of the study; therefore, there was a low risk of attrition bias. Finally, the study had a high risk of SR bias. The study was conducted in 1984; however, the trial registry numbers of RCTs became mandatory in 2005 as a requirement for a publication to be eligible (Viergever & Li, 2015). Therefore, it cannot be established whether the outcomes were changed.

Table 3: Justifications for judging the risk of bias assessment tool with quotes based on the modified Cochrane risk of bias tool (Higgins et al., 2011).

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| **Study**  **Domain** | Ågren et al.  (2006) | Berger et al.  (2007) | Momen-Heravi et al.  (2017) | Strömberg & Ågren,  (1984) |
| Random sequence generation adequate? | “Participants were allocated to each group using a computer-generated approach.” | “Selection of participants was done based on a developed inclusion and exclusion criteria and hospital patient records. There was no mention of the series of randomization used.”  “A stratified approach to randomization was used, and this was admission within 6h of injury for individuals aged between 16 and 65 years and had burns that covered >20% BSA and 10% BSA assessed as surgical on admission including healthy patients undergoing plastic surgery.” | “Randomization assignment was achieved via computer-generated random numbers.”  “Randomization was done as blindness by trained staff at the clinic that strengthened the methodology.” | “The study does not mention how the randomization of participants was achieved.” |
| Allocation concealment adequate? | “They used block sizes of four or six stratiﬁed for center that allowed equal placement of participants in each group hence the methodology's strength.” | “Third-party was used for randomization, and they kept the data.” | “The use of blindness by trained clinical staff also ensured a low risk in allocation bias.” | “There is no mention of who bore the responsibility of allocating the participants into the different groups and providing the supplement and placebo.” |
| Blinding of participants adequate? | “The study was a double-blind study; hence both the staff and participants were blinded to the treatment codes.”  “Allocation involved the use of centrally packaged, consecutively numbered, identical packages containing zinc oxide/placebo meshes.” | “the same amount of zinc supplements and the placebo was given; hence they were both unaware of the interventions used.” | “It was a double-blind study; both participants and staff were blinded to the codes, and the similarity in the zinc and placebo capsules ensured the participants and staff did not know what they were taking and giving respectively.” | “The approaches used for blinding are not mentioned in the study; hence there is an unclear detection bias.” |
| Blinding of personnel adequate? | “The investigators were required to select the next available number when a new patient came into the trial, and the codes were kept confidential until the final assessments and conclusions drawn.” | “The same amount of zinc supplements and the placebo was given; hence they were both unaware of the interventions used.” | “It was a double-blind study; both participants and staff were blinded to the codes, and the similarity in the zinc and placebo capsules ensured the participants and staff did not know what they were taking and giving respectively.” | “The approaches used for blinding are not mentioned in the study; hence there is an unclear detection bias.” |
| Blinding of outcome assessors adequate? | “The investigators were required to select the next available number when a new patient came into the trial, and the codes were kept confidential until the final assessments and conclusions drawn.” | “There was no indication of whether the assessors were blinded.” | The analysis was done independently, but the approach for blinding the assessors is not mentioned hence having an unclear detection bias. | “The approaches used for blinding are not mentioned in the study.” |
| Was incomplete outcome data addressed? | “It is not indicated on how they analyzed the intention to drop out; hence there is an unclear risk of bias.” | “The study did not mention how it dealt with those that did not complete the isotopy.” | “Highlighted a methodology that would deal with the drop put outcomes that is the Last-Observation Carried-Forward method (LOCF) which is based on the intention-to-treat (ITT) principle that reduced the possibility of attrition bias | “No patient dropped out of the study.” |
| Was it free of selective reporting? | “The checking of the trial registry number, "ISRCTN35311675" via www.controlledtrials.com website, indicated no differences in reporting.” | “The study does not provide a registration number hence a high risk of SR bias.” | “The study provides a trial registry number, "IRCT201506215623N46," which, when searched online, revealed no differences in the results in the trail and the originally intended outcomes.” | “The study was conducted in 1985; however, the trial registry numbers of RCTs became mandatory in 2005 as a requirement for a publication to be eligible. Therefore, it cannot be established whether the outcomes were changed.” |

**Interpreting the finding / Evidence Synthesis**

The research aimed to investigate the effectiveness of zinc therapy in accelerating wounds healing period. The findings of the four reviewed articles illustrated that, zinc therapy has improved the wound closure time, thus, the recovery process increased. In regard to the high quality and lower risk of bias in Cochrane risk of bias tool, Ågren et al. (2006) and Momen-Heravi et al. (2017) were high in internal validity as they show only one criteria indicated as unclear risks of bias which is incomplete outcome data (attrition bias), and blinding of the outcome assessors (detection bias) respectively (Jargensen et al., 2016). Berger et al. (2007) is considered a low-quality study because one criteria indicated as high risks of bias which is selective reporting (reporting bias), and three criteria listed as an unclear risk of bias: random sequence generation (selection bias), blinding of the outcome assessors (detection bias) and incomplete outcome data (attrition bias). Strömberg & Ågren (1984) study, is considered a poor-quality due one criteria indicated as high risks of bias: the selective reporting (reporting bias), and five criteria listed as an unclear risk of bias which is the selection bias, performance bias, directional bias and detection bias.

The evidence of this study was synthesized using the Quality Improvement Projects that developed by Melnyk & Fineout-Overholt (2011). The tool was used for the evaluation of the level of research evidence employed. This is as presented in Table 4 below. The study by Ågren et al. (2006) aimed at making comparisons of the effectiveness of topical zinc oxide with placebo mesh on secondary healing pilonidal wounds. The study’s research question through inference was whether topical zinc oxide mesh more effective in promoting secondary healing pilonidal wounds compared to a placebo mesh. The study employed a randomised, double-blind, placebo-controlled, multicentre trial methodology which is considered the “Gold Standard” in research and provides level 1 evidence in research. The rationale is that randomisation is done and both the participants and investigators are blinded and involved multiple centres. The study provided strong evidence and was done in several centres indicating that the results can be generalized to other care organizations. Therefore, based on the evidence quality the use of topical zinc can be implemented in any organization. The study by Berger et al. (2007) targeted at assessing the effects of TE supplementation on systemic substrate turnover and local protein metabolism during wound healing after major burns. The research question that guided the study was whether TE supplementation on systemic substrate turnover and local protein metabolism was effective to promote wound healing after major burns. The researchers employed prospective, randomised, placebo-controlled trial that provides level 2 evidence due to the prospective nature of the study. The study’s limitation is that it was conducted in a single institution. However, the strong evidence provided makes it applicable to any organization, hence the use of TE supplementation is recommended.

Further, Momen-Heravi et al. (2017) aimed at determining the effects of zinc supplementation on wound healing and metabolic status in patients with a diabetic foot ulcer. The study’s research question was whether zinc supplementation effective in wound healing and metabolic status in patients with a diabetic foot ulcer compared to a placebo. The researchers employed a randomised, double-blind, placebo-controlled trial that provides Level 1 evidence. The limitation of this study is that it was conducted in one organization. However, the level 1 evidence makes it genralizable to nursing practice in other organizations. Finally, the study by Strömberg & Ågren, (1984) aimed at establishing the efficacy of locally applied zinc oxide on the healing of leg ulcers compared to no application of zinc oxide. The study research question was whether locally applied zinc oxide more efficacious in promoting wound healing of leg ulcers compared to local application that does not have zinc oxide. The study also used a randomised, double-blind study that provides Level 1 evidence. The study was also conducted in one institution, hence limiting the generalizability of the findings. In addition, it's not a recent research, hence loosing its relevance in current practice. Therefore, despite the strong evidence, it is not applicable to current nursing practice. These are as summarized in Table 4 below.

*Table 4:* Evidence synthesis.

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| **Author/Date** | **Theoretical Framework** | **Research Questions/Hypothesis** | **Methodology** | **Level of Evidence** | **Limitations** | **Applicability** | |
| Ågren et al.  (2006) | The study aimed at making comparisons of the effectiveness of topical zinc oxide with placebo mesh on secondary healing pilonidal wounds. | Is topical zinc oxide mesh more effective in promoting secondary healing pilonidal wounds compared to a placebo mesh? | Randomised, double-blind, placebo-controlled multicentre trial | Level 1 | None | Yes. The study can be applied to the organization due to its strong evidence and use of multiple centres making the findings generalizable. | |
| Berger et al.  (2007) | The study targeted at assessing the effects of TE supplementation on systemic substrate turnover and local protein metabolism during wound healing after major burns. | Is TE supplementation on systemic substrate turnover and local protein metabolism effective to promote wound healing after major burns? | Prospective, randomised, placebo-controlled trial. | Level 2 | Conducted in one organization hence difficult to generalize findings | | Yes. Due to the string level of evidence it can be applied to any organization. |
| Momen-Heravi et al.  (2017) | The study aimed at determining the effects of zinc supplementation on wound healing and metabolic status in patients with diabetic foot ulcer. | Is Zinc supplementation effective on wound healing and metabolic status in patients with diabetic foot ulcer compared to a placebo? | Randomised, double-blind, placebo-controlled trial | Level 1 | Conducted in one organization hence difficult to generalize findings | | Yes. Due to the string level of evidence it can be applied to any organization. |
| Stromberg & Agren,  (1984) | The study aimed at establishing the efficacy of locally applied zinc oxide on the healing of leg ulcers compared to no application of zinc oxide. | Is locally applied zinc oxide more efficacious in promoting wound healing of leg ulcers compared to local application that does not have zinc oxide? | Randomised, double-blind study. | Level 1 | Conducted in one organization hence difficult to generalize findings.  Not a recent study. The research methods applied do not meet current research standards. | | No. The findings cannot be applied despite using level 1 evidence approach. As the research did not meet the recent study requirements placing doubts on findings. |

*Table 5:* The studies’ outcomes in improving wound healing

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| **Study**  **Outcomes** | Ågren et al.  (2006) | Berger et al.  (2007) | Momen-Heravi et al.  (2017) | Strömberg & Ågren,  (1984) |
| Zinc | Increased (p < 0.001) wound ﬂuid zinc levels to 1,540 (1,035–2,265) µM.  Decreased (p < 0.05) the occurrence of *Staphylococcus aureus* in wounds.  Serum-zinc levels increased (p< 0.001) postoperatively.  Fewer antibiotic prescriptions. | Plasma TE concentrations were significantly higher in the TE group.  In the burned areas, the skin contents of selenium (P=0.02) and zinc (P=0.03) increased by day 20.  13C enrichment ratio in burned skin was 0.363±0.094 (TE group) and (NS) after 1h and 0.592±0.153 (TE group) after 6h. | Reductions in ulcer length (-1.5±0.7) and width (-1.4±0.8). | 83% success rate. |
| Placebo | Serum-zinc levels increased (p< 0.001) postoperatively | 13C enrichment ratio in burned skin was 0.286±0.130 (V group) after 1h and 0.262±0.171 (V group) after 6 h. | Reductions in ulcer length (-0.9±1.2 cm) and width (-0.8±1.0 cm) | 425% success rate. |

Numerous studies has investigate the effectiveness of zinc therapy in accelerating wounds closure and improving the overall outcome (Lansdown, Mirastschijski, Stubbs, Scanlon, & Ågren, 2007; Lin et al., 2017). Other studies have shown that using zinc therapy can reduce the relative risk of infections and enhance a faster cells modeling (Andrews & Gallagher-Allred, 1999; Attia, Belal, El Samahy, & El Hamamsy, 2014; Henkin, 1974). Beside these studies which confirm the effectiveness of zinc therapy, the four RCTs finding in this review also does.

**Conclusion**

Wounds are a significant burden on healthcare. However, despite the efficacy of zinc supplements in promoting wound healing, the treatment modality has often been ignored by medical practitioners until recently. Despite the recent recognition of the effectiveness of zinc in wound healing, studies in the area began as early as the 1980s. Professionals in nursing are required to recommend evidence-based treatment methods. Randomised control trials such as those highlighted above provide the best evidence that can be used to implement evidence-based practices to promote wound healing. While RCTs are considered to be the most effective, it is evident that they are not full proof and may contain biases that may affect the validity and reliability of the results. However, all the studies discussed highlight that zinc is effective in

promoting wound healing; hence with this evidence, these trials can be implemented in my local health area.

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