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Review

The influence of zinc supplementation on IGF-1 levels in humans: A systematic review and meta-analysis

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ABSTRACT

The effect of supplementation with zinc on levels of IGF-1 remains relatively unexplored, and many of previous studies have reported equivocal findings. Thus, the aim of this study was to elucidate the influence of zinc on IGF-1. A complete systematic search was executed in Scopus, Web of Science, Embase, and PubMed/MEDLINE, by reviewers, from database inception until June 2019. Weighted mean difference (WMD) with the 95% CI was used for assessing the effects of zinc on IGF-1. We evaluated between study heterogeneity using the I-squared and the Q-test statistic. Ten studies reported changes in plasma levels of IGF-1. Combined results ascertained an increase in IGF-1 levels following zinc administration (WMD: 8.620 ng/ml, 95% CI: 1.126, 16.113, I^2 = 97.3%). Subgroup analyses demonstrated that zinc intake dosage ≤10 mg/day (WMD: 9.50 ng/ml, 95% CI: 1.47, 17.53) and intervention length >8 weeks (WMD: 10.08 ng/ml, 95% CI: 0.67, 19.48) significantly greater increased IGF-1 levels. The present study demonstrated that zinc supplementation can elicit significant increases in IGF-1 in humans. In addition, greater increments were observed when zinc intake dosage was ≤10 mg/day and intervention duration >8 weeks.

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1. Introduction

Zinc is a ubiquitous, divalent, metal cation that is an essential component in 10% of human proteins and is a key micronutrient in cell signaling. Zinc is found in high concentrations in the β-cells of the human pancreas, where it plays significant role in insulin and glucagon secretion (Zhao et al., 2019). The effects of zinc on human health are, however, pleiotropic, where it is involved in the activation of certain enzymes, immune response, cell growth and proliferation, and, as a co-factor, in conferring protection against oxidative stress and inflammation (Prasad and Bao, 2019). Disturbances of zinc homeostasis have been shown to be involved in various non-communicable diseases, such as type 2 diabetes, growth retardation, age-mediated macular deterioration, alcohol-related liver disorder or sickle cell anemia (Fernandez-Cao et al., 2019; Prasad and Bao, 2019). Zinc is an important factor in growth and development in humans, mainly due to its crosstalk at a cellular level with insulin-like growth factor-binding protein 3 (IGFBP-3), growth hormone (GH), and insulin-like growth factor 1 (IGF-1). Thus, it is unsurprising that zinc deficiency can result in growth retardation and impaired bone metabolism (Adriani and Wirjatmadi, 2014; Alves et al., 2012).

Insulin-like growth factor 1 (IGF-1) is a growth factor synthesized in the liver, and elicits a myriad of effects on health due to its participation in the GH-IGF-1 axis, where it is involved in tissue homeostasis, has anti-apoptotic, mitogenic, anti-inflammatory, antioxidant and metabolic actions, contributes to skeletal muscle plasticity, maintenance of muscle strength and muscle mass, neural and cardiovascular protection, development of the skeleton, possesses insulin-like effects, and is a key factor in brain, eye and lung development during fetal development (Blanco-Alvarez et al., 2015; Hellstrom et al., 2016; Maggio et al., 2013; Vitale et al., 2019). As an anabolic hormone, IGF-1 plays important roles in both growth and development, and its levels vary depending on age, with peaks generally observed in the postnatal period and at puberty (Cho et al., 2019; Rahmani et al., 2019). Via a negative feedback loop, IGF-1 levels influence the release of GH from the hypophysis (Himoto and Masaki, 2018), where some of the actions of GH include, stimulation of glucose and amino acid, cell cycle regulation, are IGF-1 dependent (Alvarez-Nava and Lanes, 2017; MacDonald, 2000).

IGF-1 levels are not constant throughout the life course but decrease with age as a reflection of the actions of GH. Following puberty, during the third decade of life, a rapid decrease in IGF-1 levels is registered. Whilst between the third and the eighth decade of life, IGF-1 levels decrease gradually, but appear unrelated to functional decline (Janssen, 2018; Newman et al., 2016; Wennberg et al., 2018).

The impact of zinc on plasma levels of IGF-1 remains relatively unexplored and many of the previous studies have shown conflicting results (Berger et al., 2015; Blostein-Fujii et al., 1997; Clark et al., 1999; Ninh et al., 1996; Rodondi et al., 2009). Thus, the aim of this study was to elucidate the influence of zinc intervention on IGF-1 levels in humans.

2. Methods

2.1. Study design and search strategy

This present study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (Moher et al., 2015). An electronic search was performed in Web of Science, Scopus, PubMed/MEDLINE, and EMBASE by the authors, from database inception until June 2019. We provided search strategy keywords in Supplementary Table 1.

2.2. Selection criteria

We followed the participant, intervention, comparison, outcome, time, and study design (PICOTS) items to define publication inclusion/exclusion criteria.

Two independent investigators screened the title and abstract of all articles to ascertain eligible studies and in the next step, reviewed the full-manuscripts of the selected studies inclusion criteria were: 1. Controlled Trial studies in human adults (either parallel or crossover designs); 2. Studies measured circulating IGF-1 at baseline and end of treatment, or reported IGF-1 change for intervention/control groups 2. Compared oral zinc administration with the control group. Moreover, studies not providing concentrations of IGF-1 pre and post treatment, animal studies, studies without a comparative group, review articles, abstracts from conferences, and commentaries were excluded.

2.3. Data extraction

Two reviewers performed the data extraction and a chief researcher resolved any disputes with discussion. Study authors, country, year of publication, sample size of studies, participants' gender, duration of intervention, mean age, study design (parallel/cross-over), zinc dosage, and averages and associated standard deviations (SD) of IGF-1 circulation at beginning, end intervention or/and alterations between beginning and end intervention.

Table 1
Characteristics of included studies.

Author	Country (year)	Participants	Duration (week)	Gender	Sample Size case/placebo	Dose
Berger et al.	USA (2015)	Premenarcheal Girls	4	female	75/75	9 mg.day
Adriani et al.	Indonesia (2014)	stunted children	24	both	12/12	0.37 mg.day
Rodondi et al.	Switzerland (2009)	FRAIL ELDERLY	4	both	25/22	30 mg.day
Az-Gomez et al.	Spain (2003)	Preterm Infants	24	both	18/16	10 mg.day
Porto1 et al.	Brazil (2000)	Children with Short Stature	24	both	18/18	5 mg.kg.day
Nishiyama et al.	Japan (1999)	Pregnant Women	8	female	17/10	34 mg.day
Hershkovitz et al.	Israel (1999)	Infants with Nonorganic Failure to Thrive	12	both	14/11	2 mg.kg.day
Blostein et al.	USA (1997)	women with noninsulin-dependent diabetes mellitus	3	female	20/20	30 mg.day
Clark et al.	UK (1999)	pubertal girls	6	female	24/19	15 mg.day
Ninh et al.	Vietnam (1996)	children	20	both	24/18	10 mg.day

2.4. Quality assessment

The quality assessment of RCT's were surveyed by means the Cochrane Collaboration's tool (Higgins et al., 2011), which composed of the following tenets: 1) allocation concealment, 2) random sequence generation, 3) incomplete outcome data, 4) blinding of participants, 5) personnel, blinding of outcome assessment, 6) selective reporting, 7) and other possible sources of biases.

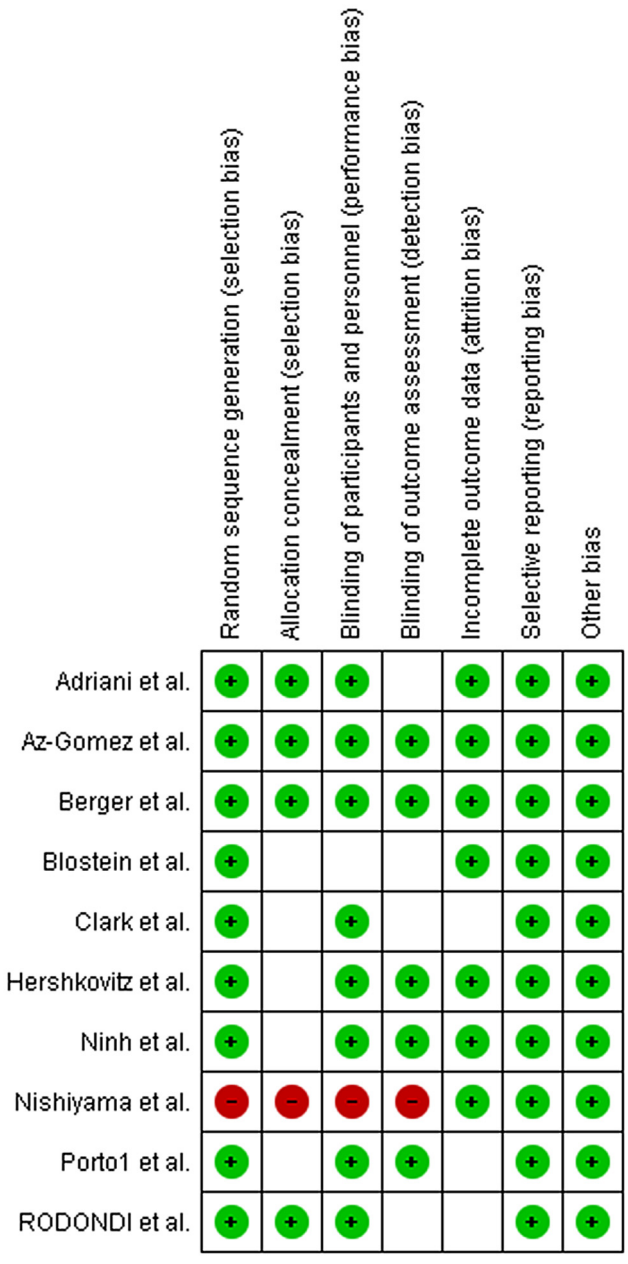
2.5. Statistical analysis

Weighted mean differences (WMD) in addition to 95% CI were used to assess effect of zinc supplementation on IGF-1 levels. If the mean change SD was not identifiable in the included trials, we utilized the next formula to calculate it: $SD_{alteration}$ = square root $[(SD_{baseline}{}^{*}SD_{baseline} + SD_{final}{}^{*}SD_{final}) - (2 \times R \times SD_{baseline} \times SD_{final})]$ (Borenstein et al., 2009). Pooled WMD from qualified trials was calculated using the derSimonian and Laird random-effects approach. We evaluated the heterogeneity between studies using the Q-test and the I-squared statistic with significant levels set at a p-value <0.10. Subgroup analyses were used to identify the sources of heterogeneity among the included studies. Publication bias was discovered through funnel plot examination, in addition to Egger's method and Begg's method, respectively. The possible impact of zinc dosage and treatment duration was assessed by means fractional polynomial approaches within non-linear dose-response analyses, in addition to conducting a meta-regression. All statistical analyses were implemented utilizing Stata program (Stata Corp. College Station, Texas, USA) and an *a priori* p-value ≤ 0.05 was used to demarcate statistical significance.

3. Results

The initial search yielded 606 studies from PubMed/Med-line, Scopus, Web of Science, and Embase. After duplicates were removed, 317 studies remained for further assessment. Following screening against inclusion criteria, 286 publications were excluded and 31 trials were eligible for full-text extraction. Subsequently, 21 studies were ruled out for the following reasons: 1) no data of interest were evident 2) and non-randomized controlled trial (RCT) design, Lastly, ten publications were inserted in the quantitative meta-analysis (Adriani and Wirjatmadi, 2014; Berger et al., 2015; Blostein-Fujii et al., 1997; Clark et al., 1999; Diaz-Gomez et al., 2003; Hershkovitz et al., 1999; Ninh et al., 1996; Nishiyama et al., 1999; Porto et al., 2000; Rodondi et al., 2009).

Table 2
Quality assessment of study included in this study.



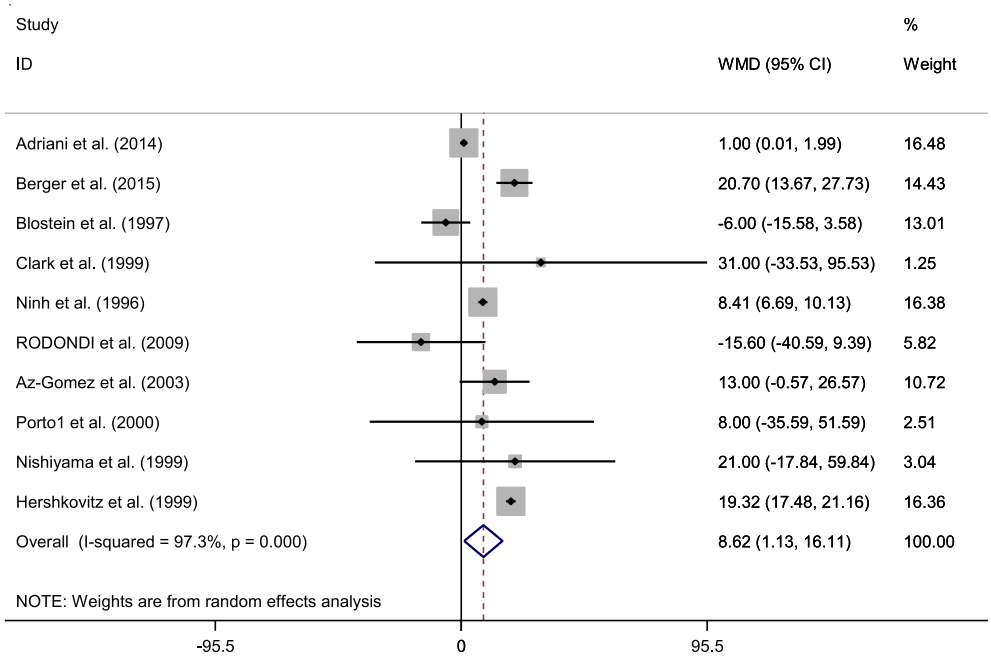


Fig. 1. Forest plot of randomized controlled trials investigating the effects of zinc supplementation on IGF-1 levels.

Table 3
Pooled estimates of effects on IGF-1 within different subgroups.

Group	No of comparisons	WMD (95% CI)	P value	P-heterogeneity	I^2 (%)
Zinc supplementation dosage (mg/day)					
≤10	6	9.50 (1.47–17.53)	0.020	0.000	98.5
>10	4	2.45 (−18.56 to 23.47)	0.819	0.304	17.5
Intervention duration (week)					
≤8	5	6.27 (−12.67 to 25.21)	0.517	0.000	83.6
>8	5	10.08 (0.67–19.48)	0.036	0.000	98.7
Type of population					
Preterm Infants	2	19.20 (17.37–21.03)	0.000	0.366	0.0
Children	5	9.26 (2.24–16.27)	0.010	0.000	94.9
adult	3	−5.48 (−17.43 to 6.46)	0.368	0.298	17.4

3.1. Study characteristics

Features of all included trials are summarized in Table 1. There were 247 and 218 sample size in zinc and control groups, respectively. Dose of zinc intervention ranged between 0.37 and 34 mg/day. Two arms were employed in the USA (Berger et al., 2015; Blostein-Fujii et al., 1997), one in Indonesia (Adriani and Wirjatmadi, 2014), one in the UK (Clark et al., 1999), one in Vietnam (Ninh et al., 1996), one in Switzerland (Rodondi et al., 2009), one in Spain (Diaz-Gomez et al., 2003), one in Brazil (Porto et al., 2000), one in Japan (Nishiyama et al., 1999) and one in Israel (Hershkovitz et al., 1999). Included studies were published between 1996 and 2015. The mean follow up of treatment was 12 weeks. All publication were clinical trials. Most publications were implemented on both genders (Adriani and Wirjatmadi, 2014; Diaz-Gomez et al., 2003; Hershkovitz et al., 1999; Ninh et al., 1996; Porto et al., 2000; Rodondi et al., 2009) and four conducted on women (Berger et al., 2015; Blostein-Fujii et al., 1997; Clark et al., 1999; Nishiyama et al., 1999). Table 2 detailed the summary results of the quality assessment of meta analyses. Three studies were of fair quality (Blostein-Fujii et al., 1997; Clark et al., 1999; Rodondi et al., 2009), 6 were of good quality (Adriani and Wirjatmadi, 2014; Berger et al., 2015; Diaz-Gomez et al., 2003; Hershkovitz et al., 1999; Ninh et al., 1996; Porto et al., 2000), and one was of poor quality (Nishiyama et al., 1999).

3.2. Meta-analysis results

Ten studies providing a total of 465 (case = 247, control = 218) individuals published alterations in IGF-1 plasma levels as an outcome measure. The random-effects model asserted an significant elevate in IGF-1 after zinc administration (WMD: 8.620 ng/ml, 95% CI: 1.126–16.113, p = 0.024; Fig. 1). Nevertheless, a significant high of heterogeneity was discovered in the meta-analysis (p = 0.000, I^2 = 97.3%).

3.3. Subgroup analysis

We stratified trials across zinc intake dosage and intervention duration (week) (Table 3). The analyses demonstrated that zinc intake dosage ≤10 mg/day (WMD: 9.50 ng/ml, 95% CI: 1.47–17.53, I^2 = 98.5%) increased IGF-1 significantly more than zinc intake dosage >10 mg/day (WMD: 2.45 ng/ml, 95% CI: −18.56–23.47, I^2 = 17.5%). Furthermore, follow up duration >8 weeks (WMD: 10.08 ng/ml, 95% CI: 0.67–19.48, I^2 = 98%) improved IGF-1 significantly more than ≤8 weeks (WMD: 6.27 ng/ml, 95% CI:

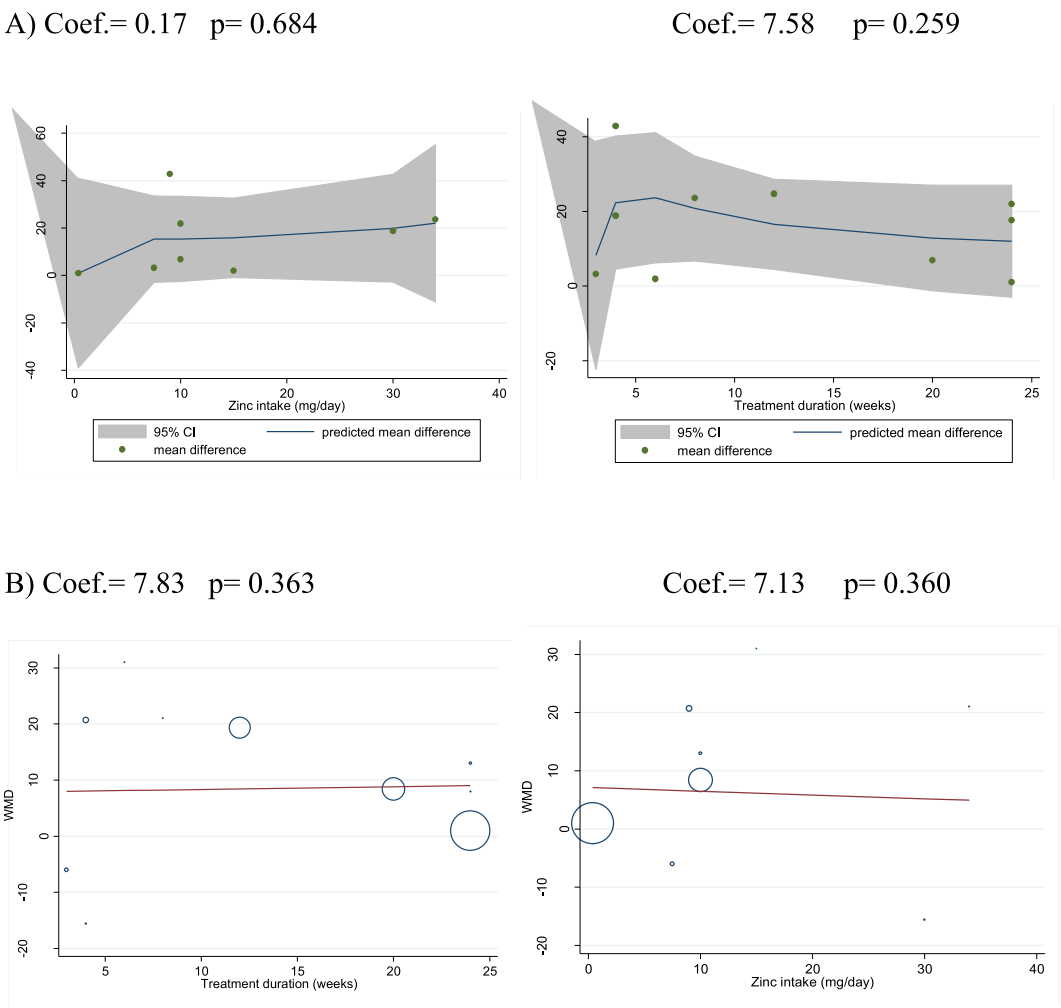


Fig. 2. A) Dose-response analysis – zinc intake dosage (mg/day) and intervention duration (week) with IGF changes. Weighted mean difference, WMD, B) Meta regression analysis (Zinc intake dosage (mg/day) and intervention duration (week) with IGF changes).

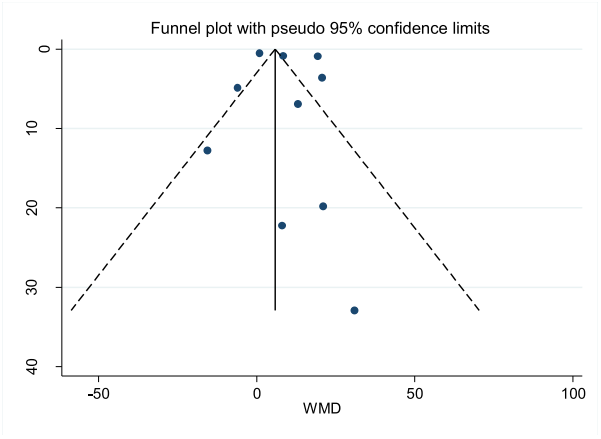


Fig. 3. Funnel plot of the weighted mean difference (WMD) versus the s.e. of the weighted mean difference (WMD).

12.67–25.21, I^2 = 83%). Additionally, among preterm infants, zinc administration resulted in a greater increase in IGF-1 (WMD: 19.20 ng/ml, 95% CI: 4.99–6.54, I^2 = 0.0%) than children (WMD: 9.26 ng/ml, 95% CI: 2.24–16.27, I^2 = 94%); however, it did not influence IGF-1 levels in adult subjects (WMD: −5.48 ng/ml, 95% CI: −17.43–6.46, I^2 = 17%).

3.4. Dose-response analysis and meta regression

Dose-response analysis and meta regression of the follow-up duration and zinc intake dosage with alterations in plasma IGF-1 did not reveal a significant association (Fig. 2).

3.5. Sensitivity analysis and publication bias

The Begg's and Egger's tests, did not highlight any publication bias in the meta-analysis (p = 0.721 and p = 0.531, respectively). Visual inspection of funnel plot also demonstrated no evidence of the presence of publication bias (Fig. 3). To explore the influence of any individual study on the pooled effect, we iteratively omitted each study and assessed the impact. Accordingly, we found no significant effects of any one trial on the overall effect.

4. Discussion

Our meta-analysis of 10 clinical trials, which included 465 subjects, revealed that zinc supplementation yields a significant rise in IGF-1 levels in humans. Our findings from subgroup analyses suggested that the effect of zinc supplementation on levels of IGF-1 in humans depends, not only on the dosage, but also on the duration of the intervention and on the age of the participants.

Our results show that daily zinc intake ≤10 mg increased IGF-1 significantly more versus a daily intake of zinc >10 mg/day. Thus,

we can infer that the dose of daily zinc is an important factor in increasing IGF-1 levels and that an excessive daily intake of zinc does not yield any considerable benefits. However, some studies have argued that zinc supplementation has no effect on IGF-1 levels. Our results contradict the findings of a prior study by Barffour *et al.* who concluded that the administration of zinc (in 7 mg tablets or micronutrient powder consisting of 10 mg zinc + 6 mg iron +13 other micronutrients) in 419 Laotian children did not increase IGF-1 levels (Barffour et al., 2019). Normal daily intake of zinc in humans is estimated at 14–30 mg/day, but values between 2.8 and 40 mg/day can, reportedly, yield physiological zinc homeostasis, whilst excess zinc is eliminated mainly via the gastrointestinal tract (Roohani et al., 2013).

Further, we showed that zinc supplementation >8 weeks increased IGF-1 significantly more versus zinc supplementation ≤8 weeks. Our findings might be related to the prior serum zinc concentrations of the subjects who were given zinc supplements, and that a supplementation of >8 weeks is required to replenish zinc deposits in zinc deficient patients. Zinc supplementation increases IGF-1 levels in both zinc-deficient and normal, non-zinc-deficient, subjects (Rocha et al., 2015). However, previous reports have asserted that zinc supplementation is more effective in patients who have a zinc deficiency and non-normal serum zinc levels. Park et al. studied the effect of zinc supplementation on IGF-1 levels in children diagnosed with failure-to-thrive; however, study cessation, they found no significant modifications in serum IGF-1 levels in these participants, attributing this result to the fact that the study group had normal zinc and IGF-1 values prior to the zinc intervention (Park et al., 2017).

The most prominent finding of the present study was that the influence of zinc supplementation on IGF-1 levels depends on the age category in which the intervention was delivered. Among preterm infants, zinc administration resulted in a greater increase in IGF-1 levels versus children, whereas it did not influence IGF-1 levels in adults. Firstly, these results confirm the hypothesis of Akram et al., that zinc is an essential factor in preventing premature birth (Akram et al., 2011). Zinc is an essential trace element for human health, earning its colloquial title of '*the metal of life*', due to its participation in cell growth, immunity, tissue repair, synthesis of proteins and of the DNA, thyroid gland and optimal bone functioning (Kaur et al., 2014; Maggio et al., 2013). Along with proteins, phosphorus, magnesium, sodium and potassium, zinc is a type 2 nutrient whose deficiency results in the inhibition of linear growth (Millward, 2017). Zinc is required as early as fetal-placental development, where subjects who are small for their gestational age have lower body mass index, hemoglobin, iron, zinc and placental protein levels of IGF-1 as compared to infants measured as large for gestational age group (Akram et al., 2011). Thus, the authors suggested that zinc supplementation in pregnancy might decrease preterm birth risk, and elicit a positive impact on the outcome of the pregnancy and on the infant's birthweight (Akram et al., 2011). Interestingly, in murine models with zinc deficiency, IGF-1 levels can be corrected by stimulating caloric intake or by external administration, but these measures do not correct the growth retardation (MacDonald, 2000).

Our results reinforce the concept that zinc supplementation provides benefits in children with growth disturbances related to zinc deficiency. Hamza et al. demonstrated that zinc supplementation leads to an increase in IGF-1 levels in Egyptian children who had a serum zinc deficit and short stature. In Hamza et al, the authors administered zinc supplements for a period of 3 months in 50 zinc-deficient pre-pubertal children and observed an elevate in serum zinc in 100%, IGF-1 concentrations in 40% and IGFBP-3 levels in 40% of the study group, respectively, as well as an elevation of the height standard deviation score. However, despite the zinc supplementation, normal ranges of serum zinc, IGF-1 and IGFBP-3 were only noted in 64%, 40% and 22% of the children, respectively. Thus, an intervention >3 months might have been required in these children to normalize the concentrations of serum zinc, IGF-1 and IGFBP-3 (Hamza et al., 2012). Imamoglu *et al.* also confirmed the stimulatory effect of zinc treatment on IGF-1 levels, where 22 pre-pubertal children who received zinc supplements for 6 weeks registered an elevate in IGF-1 and IGFBP-3 concentrations as compared to baseline. On the other hand, children who had normal zinc levels and continued zinc supplementation for 6–12 months did not register higher standard deviation scores for weight or height, implying that zinc supplementation provides greater benefits mainly in zinc-deficient subjects (Imamoglu et al., 2005).

We also demonstrated that zinc supplementation at an older age did not increase IGF-1 levels. Maintaining high or low levels of IGF-1 in adults and the elderly remains a controversial topic, lacking consensus. Zinc is a micronutrient of paramount importance to the bioactivity of IGF-1, nevertheless, it should be taken into account that an increased bioactivity of IGF-1 has been linked to several types of malignancies, such as breast, prostate or colorectal cancer (Rahmani et al., 2019). On the other hand, there is evidence suggesting that higher IGF-1 are cardio- and neuroprotective and thus beneficial (Janssen, 2018). Contrastingly, a meta-analysis by Burgers *et al.* suggested that, in adults, both decreased IGF-1 and increased IGF-levels are linked to increased all-cause mortality. Their research included 12 studies enrolling 14,906 subjects and demonstrated, using a dose–response meta-regression, that there is a U-shaped relationship between all-cause mortality and IGF-1 levels ($P = 0.003$), as well as cardiovascular and cancer-related mortality (Burgers et al., 2011; Gunawardane et al., 2015). In adults, the effects of zinc on IGF-1 seem to have a different outcome versus children. These observations might be attributed to the installment of the somatopause during which GH and IGF-1 levels gradually decrease (Maggio et al., 2013). Thus, further studies are necessary to elucidate the roles of IGF-1 in health and disease, as well as the crosstalk between zinc supplementation and IGF-1 in humans.

Our study has several limitations, however; for instance, there was large heterogeneity in study design, where a wide array of zinc dosages, and study durations were employed. Moreover, the studies included a range of subjects and ages, including women with noninsulin-dependent diabetes mellitus, frail elderly, children and preterm infants, all of whom may conceivably demonstrate differing concentrations of IGF-1, although this issue is, at least in part, moderated by considering modifications from baseline. Moreover, despite these heterogeneities, the random-effects model methodology used in the present study represents a significant benefit in being able to control for such factors. In addition, according to the results of current study, more studies are needed in relation to zinc intake in the elderly, because zinc supplementation may be associated with prolonged life and aging process.

5. Conclusion

The present study highlighted that zinc supplementation leads to a significant increase in IGF-1 in humans. In addition, greater increments were observed when zinc intake dosage was ≤10 mg/day and intervention duration >8 weeks.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jksus.2020.01.018.

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