

# Quality of the Effect of Chelated Chromium on Selected Serum/Plasma Metabolites in Dairy Cattle

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## Abstract

The impact of supplementing chelated chromium (Cr) in transition cows has increased recently. The objective of this study was to conduct a systematic review of randomized controlled trials to evaluate the effectiveness of supplementation of chelated chromium (Cr) on plasma glucose, non-esterified fatty acid (NEFA) and insulin during the transition period in dairy cows. A total of 322 transition dairy cows, belonged to seven studies from five papers, were used. The complete steps of meta-analysis were performed according to the standard pathway of PRISMA. For this reason, a comprehensive meta-analysis was used to accomplish this mission. The effect model and I<sup>2</sup> statistic was used to estimate the degree of heterogeneity. Forest plot was used to present a graphic means and their confidence intervals, and a heterogeneous degree was explored with meta-regression, also Begg's test was conducted to investigate the publication bias. Estimated the effect size of chelated Cr on glucose, NEFA, and insulin outcomes during the three-time points (i.e. before, at, after calving) was no significant (glucose ES=(0.049-0.078) 0.015, p-value=0.649; NEFA ES=(-0.719-0.45) -0.134, p-value=0.653; and insulin ES=(-0.090-0.154) 0.032, p-value=0.611. The heterogeneity was not significant for all variables (glucose I<sup>2</sup>=0, p-value=0.981; NEFA I<sup>2</sup>=0 p-value=1; and insulin I<sup>2</sup>=0, p-value=0.980). Consequently, fixed-effects models were used for the analysis of such data. Furthermore, Begg's test indicated no evidence of substantial publication bias for all parameters. The influence analysis showed that the removal of any study did not change the direction or significance of point estimates. The meta-analysis of our study indicated that chelated Cr supplementation of diets of dairy cows during the transition period provided a glucose tolerance effect by increasing the insulin response and decrease NEFA concentration, but not in a significant level.

**Keywords:** chelated chromium, dairy cattle, meta-analysis, plasma/serum metabolites, transition period

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## 1. Introduction

Chromium (Cr) is an essential micronutrient that can reduce the risks of neuropathy, infertility, immune malfunction, arteriosclerosis, hypercholesterolemia and hyperlipidemia, and cell metabolism and death [1]. The demand for Cr is typically increased during different forms of

nutritional, metabolic, physical stress, and had effects on nutritional metabolism [2].

Chromium is biologically active as a part of a biomolecule called chromodulin, which is a part of insulin signaling pathway and appears to affect the carbohydrate and lipid via the action of insulin [3]. It is therefore crucial for normal carbohydrate, lipid, and protein metabolism [4]. It can be chelated

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with methionine, picolinate, propionate and yeast [5], while the most stable oxidizing form is the trivalent chromium (Cr<sup>3+</sup>) which is found in living organisms and is well-thought-out to be a highly safe form of Cr [6].

The trophic effect of Cr is to enhance communication between insulin and its receptors located on the cell membrane of insulin-sensitive tissues by increasing membrane fluidity and rate of insulin internalization as glucose tolerance factor [7]. Mononuclear cells from dairy cows supplemented with Cr in the ration was found to produce a low concentration of cytokines interleukin 2, interferon, and TNF- $\alpha$  [8].

Several studies conducted during the transition period and early lactation have demonstrated that cows fed supplemental Cr have increased milk yield and improved energy metabolism, as measured by low circulating concentrations of NEFA, and increased plasma insulin concentration that is a glucose tolerant factor [9]. Along with the increase milk yield, serum NEFA concentration decreased with Cr supplementation by increased the dry matter intake as the Cr supplementation from 21 days prepartum to 35-day postpartum increased rates of lipogenesis and decreased the net lipolysis [3, 10].

Meta-analysis is a quantitative, formal, an epidemiological study used to assess systematically previous research studies to derive conclusions about that body of research [11]. Subsequently, a consolidated and quantitative review of such large, and complex studies is obtained [12]. The examination of variability or heterogeneity results obtained by previous studies is also a critical outcome of the meta-analysis [13]. The objective of this study was to conduct a systematic review of randomized controlled trials to evaluate the effectiveness of supplementation of chelated Cr on plasma metabolites, especially glucose, NEFA and insulin in dairy cows during the transition period.

## 2. Materials and methods

### *Selected studies*

This review considered all publications reporting reference values for the assessment of Cr effect on plasma metabolites during the transition period.

### *Types of reference individuals*

All of the studied cows were on transition period and free from pathological ailments that are related to the reproduction, milk production and metabolic performance.

### *Inclusion and exclusion criteria*

#### *Inclusion criteria*

- Availability of English version of the paper in the case of foreign – language articles.
- All cows on a transition period which were determined as four 4 weeks around the time of calving.
- All cows were only treated by chelated Cr.
- Estimation of plasma glucose, insulin, NEFA.
- A control group (Zero doses) on every study was included for comparing and verifying the effect of Cr on the selected plasma metabolites.

#### *Exclusion criteria*

- Presentation of reference values that had already been included in a previously published article.
- Studies that depend on beef cows, calf or dry off cows
- The comparison study which depends on the parity
- Studies that present on the mid and late lactation only or early lactation without parturition and late pregnancy
- Using concomitant treatment with chelated Cr
- The presence of production or pathological ailments

### *Searching strategy and selection of studies*

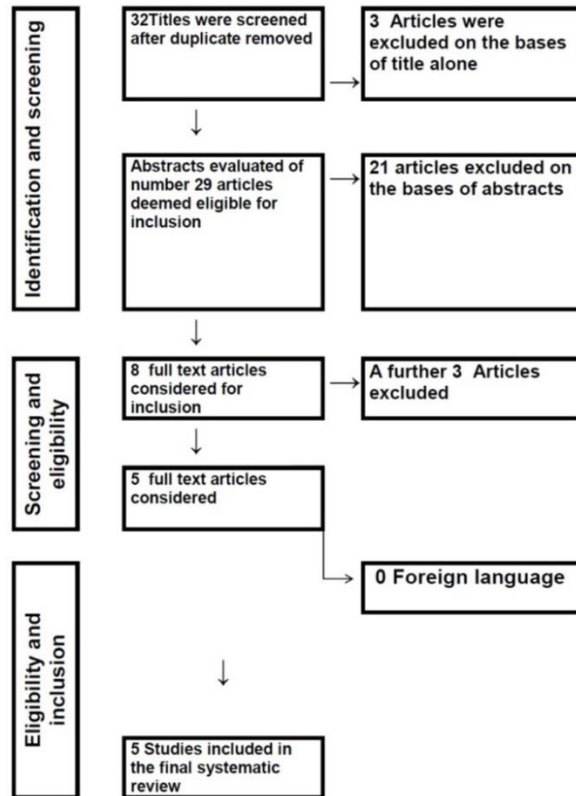
The aim was to search for all published papers dating back to the start of studies examined the effect of Cr on the cow metabolic performance in comparison with non-treated cows. We searched the PubMed, Ovid, Sage, Scopus, and ISI web of knowledge database with a combination of the following search terms TRANSITION PERIOD (title/abstract), and CHROMIUM (title/abstract), METABOLIC PERFORMANCE (title/abstract), DAIRY COWS (title/abstract) from the earliest data until August 2019. This process was complemented by reviewing citation, searching with Google Scholar, expert referrals, and hand-searching. We combined the outputs from the databases using a referencing program, EndNote (version X7; Thomson Reuters). The articles included in this study were shown in Table 1.

*Data extraction and analysis*

We extracted the following data: the source and the year of study, type of chelated Cr, number of treated and non-treated animals, treated doses, duration of the study, and the result of mentioned parameters i.e., glucose by mg/dl, NEFA by mmol/l, and insulin by  $\mu\text{U/ml}$ .

*Quality assurance*

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14]. All available published papers on assessment of Cr effect on plasma metabolites during the transition period on cows free from pathological diseases related to the reproduction, milk production and metabolic performance.



**Figure 1.** Identification, screening, eligibility and finally selected papers on the effect of chelated chromium on selected serum/plasma metabolites in dairy cattle during the transition period

*Statistical analysis*

For the statistical meta-analysis, a commercial software program for meta-analysis was used (Comprehensive meta-analysis version 3, USA). The effect of chelated Cr on the selected blood metabolites was evaluated by meta-analysis using the fixed and random effect model, 95% confidence intervals, and statistical significance of effect size. The effect size was conducted using a standardized Z-statistic. All outcomes that weighted mean difference of treatment relative to control were calculated to show the specific value of the effect of chelated Cr on the outcomes of dairy cattle during the transition period using p-

value [15].  $I^2$  statistic was used to estimate the degree of heterogeneity which describes the total variation which depends on Q-statistic and the number of trials (K). A negative value of  $I^2$  put equal to zero; while the values between 0 to 100% and equal or more than 50% are considered heterogeneous [16].

$$I^2 = \frac{Q - (K - 1)}{Q} \times 100$$

Study weight was calculated based on the inverse square of the standard error of the effect of each trial. Forest plot was used to present the means and their confidence intervals graphically and the heterogeneous degrees were explored with meta-regression [15], also Begg's test was conducted to investigate the publication bias [17].

3. Results and discussion

A summary of the papers used for the meta-analysis was provided in a descriptive table (Table 1) which include the study name, time points, the number of trials, type of chelated Cr, the doses, outcomes names (glucose by mg/dl, NEFA by mmol/l, BHB by mmol/l, and insulin by  $\mu$ U/ml), the treated and control outcomes results and the number of cows. Our meta-analysis study included five studies with seven trials depending on the excluded and included criteria, trials depended on numbers of doses used in each study at different time points during the transition period.

Overall trials analyzed, there was no significant effect of chelated Cr on plasma or serum glucose, NEFA, insulin depending on our meta-analysis effect size (ES) (95% CI)—comparing with the control cows—(glucose ES=(0.049-0.078) 0.015,  $p$ -value=0.649; NEFA ES=(-0.719-0.45)-0.134,  $p$ -value=0.653; and insulin ES=(-0.090-0.154) 0.032,  $p$ -value=0.611. A forest plot for the impact of chelated Cr on plasma or serum glucose, NEFA, and insulin was presented in figures 2, 3, and 4, respectively. There was no heterogeneity between supplemented and control cows in the response of

chelated Cr on plasma or serum glucose, NEFA, and insulin, as the Q- statistics indicated not heterogeneous by a random and fixed model during different time points of the study (glucose  $I^2=0$ ,  $p$ -value=0.981; NEFA  $I^2=0$   $p$ -value=1; and insulin  $I^2=0$ ,  $p$ -value=0.980). There was also no significant effect size and heterogeneity of chelated Cr on selected plasma/serum metabolites by regrouping our study according to the time that was divided into three time points (i.e. before calving, at calving, and after calving) (Table 3). Therefore, it was not necessary to do the meta-regression and the models for variables were evaluated by fixed effect. The results of Begg's test for publication bias was not significant for all of the variables (Table 4). Figures 5, 6, and 7 showed the funnel plot of the effect of glucose, NEFA, and insulin, respectively. An almost equal number of studies were found on every side of the overall effect size estimate. This indicated no publication bias found among the studies. The sensitivity analysis of any single study did not change the direction of the effect of any analysis and did not change the overall effect size estimates.

Table 1. Descriptive statistics for the effect of chelated Cr on dairy cows during the transition period

Study name	Type	Trial No.	Time	Dose mg	Out comes names											
					Glucose (mg/dl)				NEFA (mmol/l)				Insulin ( $\mu$ U/ml)			
(Hayirli et al., 2001)	Methionine	3	Before calving	0.03	63.3	10			0.247	10			16.5	10		
				0.06	61	10	58	10	0.228	10	0.289	10	16.6	10	13.7	10
				0.12	59.7	11			0.149	11			16	11		
			After calving	0.03	49.3	10			0.618	10			5.1	10		
				0.06	45.5	10	49.7	10	0.669	10	0.605	10	5.3	10	9.8	10
				0.12	53.2	11			0.506	11			6.6	11		
(Soltan, 2010)	Organic	1	2w before		64.7		65.4		0.55		0.79		6.71		5.53	
			2w after	6	59.9	60	57.5	60	0.43	60	0.61	60	5.24	60	3.67	60
			4 w after		56.9		55.5		0.36		0.54		9.93		7.31	
(Khalil et al., 2011)	methionine	1	2 w before		18		18.1		-		-		10.6		11.7	
			1 w after	50	27.8	10	33.1	10	-	-	-	-	12.8	10	12.0	
			4 w after		17.1		25.3		-		-		18.2		15.7	
					1											
(Kafizadeh et al., 2012)	L - methionine	1	1w before		51.4		46.3		0.358		0.781		13.7		11.3	
			At calving	8	52.9	30	50.9	30	0.708	30	0.799	30	9.04	30	8.45	30
			3w after		50.2		46.4		0.484		0.796		9.67		6.12	
(Yasui et al., 2014)	propio	1	Before calving		63.7		63.4		0.184		0.21		13.4		12.5	
			After calving	8	56.6	30	56.5	31	0.73	30	0.684	31	5.11	30	5.53	31

**Table 2.** Summary of effect size of chelated Cr on selected plasma or/serum parameters in dairy cows during transition period

Outcomes names	Std mean differences	Vari-ance	Number of cows		Trials (K)	Trial Sites	Effect size (95% CI)	Effect size (95% CI) p-value	Z- value	Q- value	I <sup>2</sup> (95% uncertainty interval)	I <sup>2</sup> (95%CI) p-value	SE
			treated	control									
Glucose (mg/dl)	(-0.049-0.078) 0.015	0.001	161	161	7	17	(0.916-1.153) 1.027	0.646	0.459	6.578	0	0.981	0.021
NEFA (mmol/l)	(-0.719-0.451)- 0.134	0.089	151	151	6	14	(0.271-2.267) 0.784	0.653	-0.449	0.232	0	1	1.628
Insulin (μU/ml)	(-0.090-0.154) 0.032	0.004	161	161	7	17	(0.849-1.321) 1.059	0.611	0.508	6.638	0	0.980	0.062

**Table 3.** Summary of effect size of chelated Cr on selected plasma or/serum parameters in dairy cows during transition period according to the time point

Glucose (mg/dl)									
Time point	No of study	ES interval	95%CI	p-value	Z-value	Q-value	I <sup>2</sup>	I <sup>2</sup> p-value	Standard error
Before calving	7	(0.875-1.254)	1.048	0.613	0.506	1.191	0	0.97	0.035
At calving	1	(0.686-1.6)	1.048	0.829	0.216	0	0	1	0
After calving	6	(0.859-1.184)	1.009	0.106	0.378	5.284	0	0.680	0.031
NEFA (mmol/l)									
Time point	No of study	ES interval	95%CI	p-value	Z-value	Q-value	I <sup>2</sup>	I <sup>2</sup> p-value	Standard error
Before calving	6	(0.094-4.49)	0.648	0.660	-0.439	0.068	0	1	3.892
At calving	1	(0.036-21.7)	0.886	0.941	-0.074	0	0	1	0
After calving	4	(0.212-3.366)	0.845	0.811	-0.239	0.111	0	1	2.018
Insulin (μU/ml)									
Time point	No of study	ES interval	95%CI	p-value	Z-value	Q-value	I <sup>2</sup>	I <sup>2</sup> p-value	Standard error
Before calving	7	(0.834-1.56)	1.141	0.411	0.823	0.463	0	0.998	0.104
At calving	1	(0.414-2.77)	1.072	0.886	0.143	0	0	1	0
After calving	6	(0.699-1.356)	1.237	0.873	-0.160	5.710	0	0.680	0.131

Meta-analysis is a useful tool that can be used to summarize the effects of treatment across previous studies and investigate factors explaining potential heterogeneity of response [18]. In the present study, a meta-analysis was used to investigate the potential effect of supplementing chelated Cr on selected plasma/serum metabolites in dairy cattle during the transition period which was determined in our study as 4 weeks around the time of calving. The reliability of this analysis was released by adequate statistical power derived from the number of trials, the strict criteria of selected studies, and the number of cows evaluated either treated or controlled.

The fixed effect was used to conduct the analysis. The meta-analysis should incorporate the study

effect and its interaction effects as random components of both models [19]. In this study analysis, the heterogeneity among studies was not significant, implying that the study effect is small and the difference among the studies has no effect. It has been reported that if I<sup>2</sup> is more than 50%, there is a significant heterogeneity and the random effect model should be used [16].

Unexpectedly, there was no significant effect of chelated Cr on glucose, NEFA, and insulin in our meta-analysis study comparing with the controlled group during the transition period and there was no significant heterogeneity between our included studies, this may be due to the low number of studies, trials and the studies dose that was low and nearly similar.

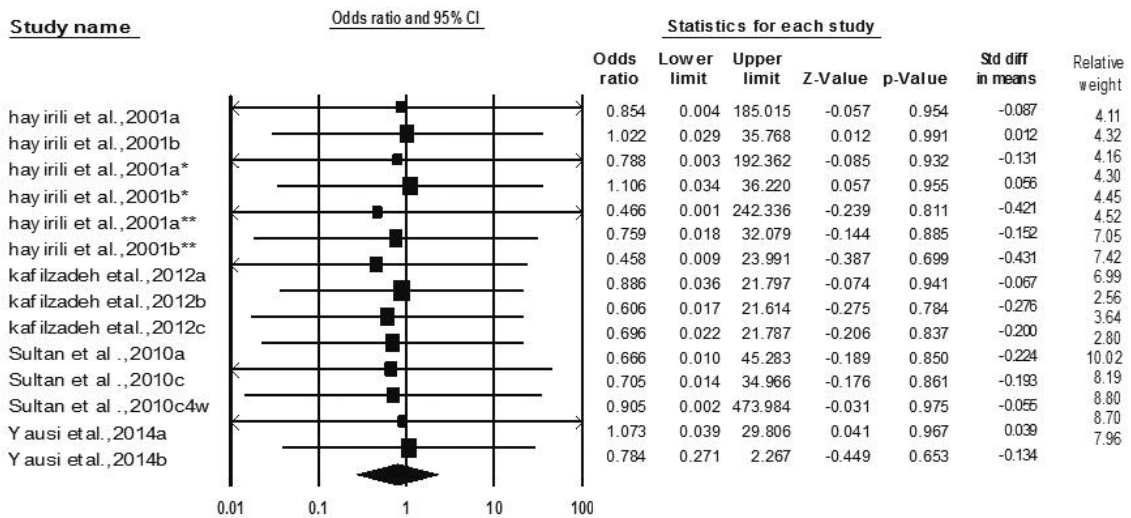


Figure 2. The forest plot of the effect of chelated Cr on serum/plasma glucose on dairy cattle during the transition period, the x-axis shows the odds ratio using z-statistic

Legend:

- The length of the horizontal line represents the 95% CI for the effect size of chelated Cr on glucose
  - The size of the square in the center is proportional to the weight assigned to the study and the specific values are listed in the following row
  - The diamond at the bottom closed to the solid vertical indicated to the little effect of chelated Cr on glucose.
- a: before calving, b: at calving, c: after calving, \*: the second trial, \*\*: third trial, 4w: 4 weeks after calving, Std diff in means: standard mean in difference

The effect of time on our study may be the main reason for the non-significant effect. For example, [2] reported that Cr treatment vs. the time on the selected serum metabolites is not significant. [20] also stated that the effect of Cr treatment on serum NEFA was not consistent across time that serum NEFA was reduced before calving by Cr treatment but not be affected after calving. But the same authors demonstrated that there was no significant effect of Cr on glucose before and after calving. Glucose and insulin is not affected by Cr-methionine supplementation, that may be due to the inability of Cr to affect the secretion of insulin from pancreas [21]. The effect of Cr on cortisol production is still unknown; but it is clear glucocorticoids which inhibit insulin secretion. The same authors stated that Cr is a glucose tolerance factor which potentiates the action of

insulin it may inversely inhibit cortisol secretion. The Cr is believed to increase insulin action in insulin-sensitive tissues (i.e., adipose and muscles [22]). Evidence suggests that Cr could enhance insulin action by binding to a low molecular weight oligopeptide (chromodulin), causing amplification of insulin receptor tyrosine kinase activity [23], resulting in an increase of farm animal production through the improvement of feed intake, growth rate, reproductive parameters and immune functions [22]. In relation to food and feed safety, there are numerous studies that come to contribute to this field [25]. Nevertheless, it is still warranted to further conduct a systematic review to evaluate the impact of excessive energy intake and chelated Cr supplementation on productive and reproductive parameters of high-producing dairy cows [24, 26].

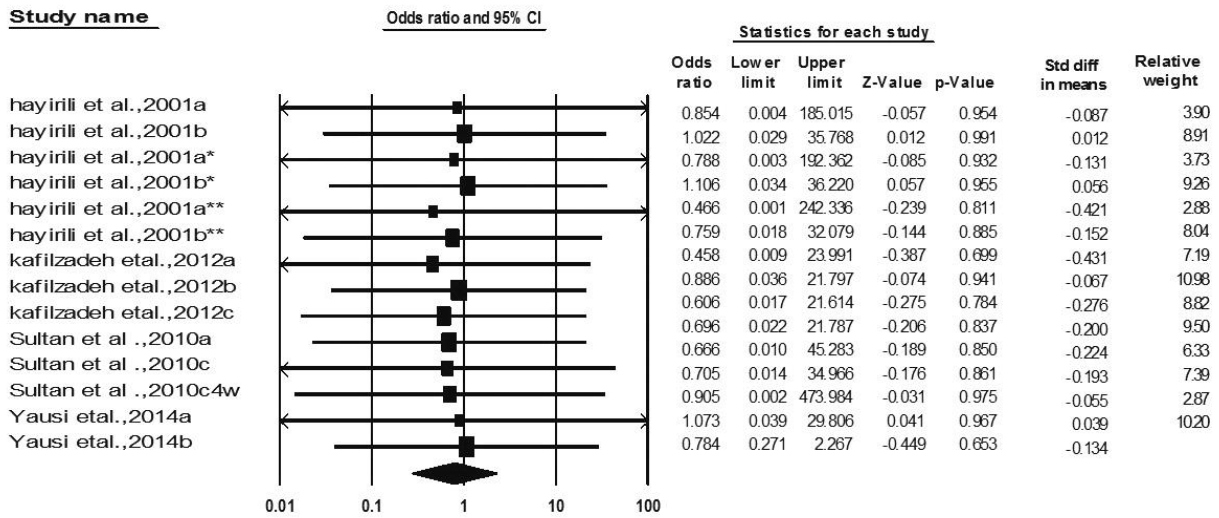


Figure 3. The forest plot of the effect of chelated Cr on serum/plasma NEFA on dairy cattle during the transition period, the x-axis shows the odds ratio using z-statistic

Legend:

- The length of the horizontal line represents the 95% CI for the effect size of chelated Cr on NEFA
  - The size of the square in the center is proportional to the weight assigned to the study and the specific values are listed in the following row
  - The diamond in the bottom closed to the solid vertical indicated to the little effect of chelated Cr on NEFA.
- a: before calving, b: at calving, c: after calving, \*: the second trial, \*\*: third trial, 4w: 4 weeks after calving, Std diff in means: standard mean in difference

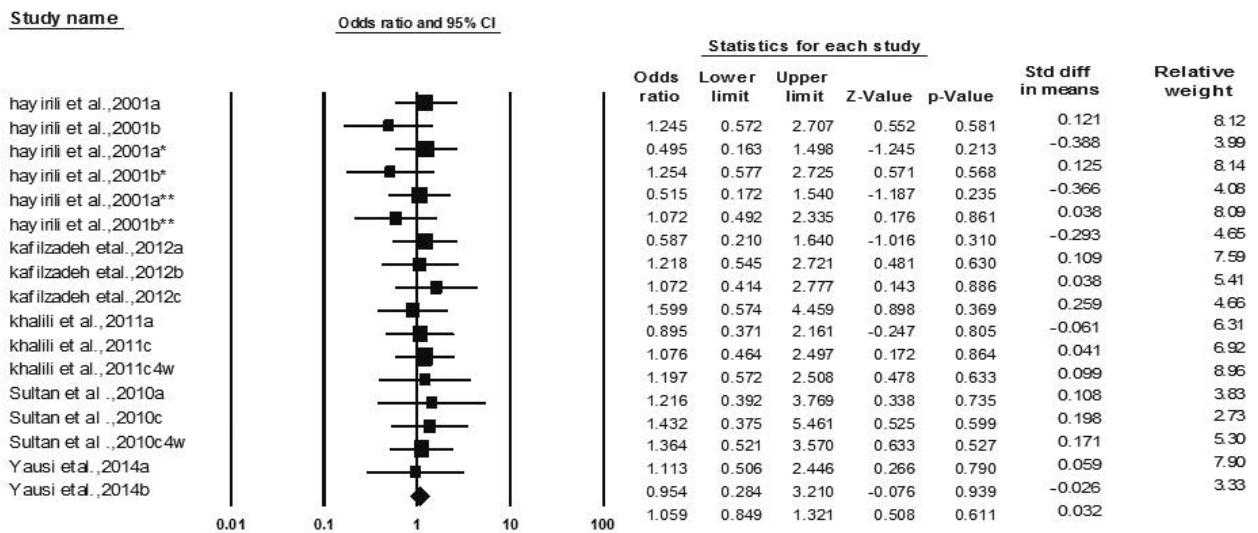
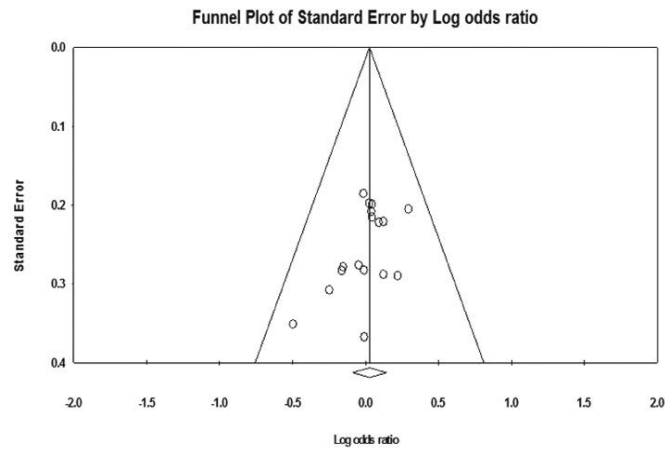


Figure 4. The forest plot of the effect of chelated Cr on serum/ plasma insulin on dairy cattle during the transition period, the x-axis shows the odds ratio using z-statistic

Legend:

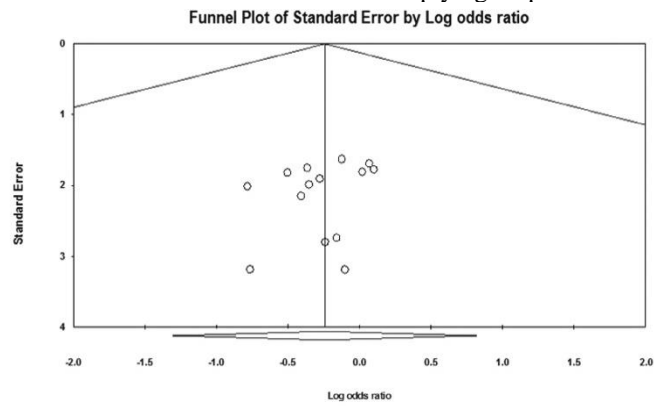
- The length of the horizontal line represents the 95% CI for the effect size of chelated Cr on insulin
  - The size of the square in the center is proportional to the weight assigned to the study and the specific values are listed in the following row
  - The diamond in the bottom closed to the solid vertical indicated to the little effect of chelated Cr on insulin
- a: before calving, b: at calving, c: after calving, \*: the second trial, \*\*: third trial, 4w: 4 weeks after calving, Std diff in means: standard mean in difference



**Figure 5.** Begg's funnel plot with pseudo 95% confidence limits of chelated Cr on glucose

*Legend:*

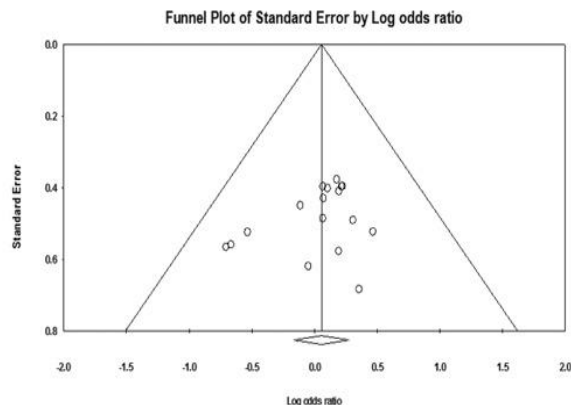
- The x-axis shows the standard error of the effect size and y- axis shows the odds ratio of the effect of chelated Cr on glucose
- The horizontal line represents the overall effect size estimated
- The 2 diagonal lines indicate an estimate of 95% CI of effect size estimate. An almost equal number of studies were found on every side of the overall effect side estimate. Implying no publication bias between studies.



**Figure 6.** Begg's funnel plot with pseudo 95% confidence limits of chelated Cr on NEFA

*Legend:*

- The x-axis shows the standard error of the effect size and y- axis shows the odds ratio of the effect of chelated Cr on NEFA
- The horizontal line represents the overall effect size estimated
- The 2 diagonal lines indicate an estimate of 95% CI of effect size estimate. An almost equal number of studies were found on every side of the overall effect side estimate. Implying no publication bias between studies.



**Figure 7.** Begg's funnel plot with pseudo 95% confidence limits of chelated Cr on insulin

**Legend:**

- The x-axis shows the standard error of the effect size and y-axis shows the odds ratio of the effect of chelated Cr on insulin
- The horizontal line represents the overall effect size estimated
- The 2 diagonal lines indicate an estimate of 95% CI of effect size estimate

An almost equal number of studies were found on every side of the overall effect size estimate. Implying no publication bias between studies.

**4. Conclusions**

The meta-analysis of our study indicated that chelated Cr supplementation of diets of dairy cows during the transition period has provided a glucose tolerance effect by increasing the insulin response and decreasing the NEFA concentration but not in a significant level.

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