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Original article

The effect of coffee-enriched chlorogenic acid on insulin, GIP and GLP-1 levels in healthy humans: a systematic review

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Summary. *Background:* There are different supplements in the drug stores in order to prevent and treat some diseases. Chlorogenic acid is one of the polyphenolic compounds affected insulin, GIP and GIP-1 to animal study as the prevention factors for diabetes, while human studies show conflict results in this regard. As regard to the lack of systematic review investigated on this topic, the purpose of this study is to assess this issue. *Materials and Methods:* Systematic search was conducted in the databases of google scholar, Science direct, PubMed and web of knowledge by the end of Feb. of 2017. Keywords for the pub med database included: "Chlorogenic Acid", "Green coffee", "Coffee", "GIP", "GLP-1" and "Insulin". Also, the qualitative assessment of studies was done by the jadad table. *Results:* 1631 studies were found, after the searching based on research literature. Then, 8 studies were entered into the qualitative synthesis stage after classifying studies based on duplication and eligibility criteria. The results of studies showed no significant effect of the chlorogenic acid in the form of coffee extracts on blood insulin concentration. In additions, GIP was decreased in one study and GLP-1 was increased in another one study, due to the use of coffee extracts-enriched chlorogenic acid. *Conclusions:* Our findings demonstrated that the consumption of Chlorogenic acid may be has lowering effect on GIP, and increasing effect on GLP-1, while has not effect on insulin, but as regard to the lack of enough studies, it has needed further study in future.

Keywords: Chlorogenic Acid, Coffee, Insulin, GIP, GLP-1

Introduction

According to the recent studies, the prevalence of disease related to endocrine systems is increasing worldwide (1). Results of the recent studies show that there is a direct relationship between mortality rate and endocrine system disorders, like diabetic patients compared to the healthy subjects (2-4). Diabetes is known as one of the hormone-related disorders, so that four hundred and forty million adults are expected to be affected by this disease, in the end of the year 2030 (5,6). The risk of some diseases, like stroke, cardiovascular, macrovascular and microvascular diseases (nephropathy and retinopathy) is high in diabetic patients. Due to it, therapeutic problems are created and extreme costs are imposed to the healthcare system of societies (7-12).

The different types of herbal supplements are presented in the drug stores, due to the high prevalence of some diseases, and also the preventing and treating of them. Chlorogenic acid (CGA) is one of these compounds with the trade name of Svetol which affect insulin, GIP and GLP-1. Also, CGA is known as one of the polyphenol compounds obtained from the extraction of green beans coffee. The functional groups of CGA are hydroxycinnamic acids, p-coumaric acid, caffeic acid, quinic acid and ferulic acid (13-17). Overall, there is a high amount of CGA in drinks containing

coffee and is used as the main compound in the herbal medicine of china which has an important role in the treatment of some diseases like cardiovascular and viral diseases (18-21). In addition, CGA has antimicrobial, anticancer and antioxidant effects (22,23). According to the conducted studies, CGA affects the metabolism of insulin, GIP, and GLP-1 hormones through several important mechanisms. One of the mechanisms is the controlling Intestinal α-glucosidase enzyme, when this enzyme is prohibited, glucose absorption is decreased and the secretion of GIP/GLP-1 is increased. As a result, the rate of gastric emptying is decreased and insulin secretion is modulated (14,16,24). In additions, CGA regulates blood glucose level and insulin hormone by decreasing activity of the liver Glucose-6-phosphatase enzyme and the increasing transport of the glucose in muscles (GLUT 4) (25,26). Due to the lack of similar studies in this regard, our purpose in this study is the assessment of the effect of coffee-enriched CGA on insulin, GIP and GLP-1 concentration in healthy subjects.

Methods

We followed the preferred reporting items for systematic reviews and the current study recorded in the international prospective register of systematic reviews (CRD42017060785).

Search Strategy

In this study, the literature search was performed through Google scholar, Science direct, web of knowledge, and PubMed databases and it was complemented by publisher databases such as Wiley online, Elsevier and springer link until February 2017. Also, the reference list of suitable articles was reviewed for the supplementary data and no language was restricted in the literature search. The key words used during searching for PubMed database were: "Chlorogenic Acid", "Green coffee", "coffee", "caffeic acid", "green coffee bean extract", "Svetol", "hydroxycinnamic acid", "quinic acid", "p-coumaric acid", "Frulic acid", "prune", "blueberry", "calluna vulgaris" and "GIP", "gastric inhibitory polypeptide", "glucose-dependent insulinotropic polypeptide", "glucose indicator protein", "GLP-1", "glucagon-like peptide 1", "Insulin", "Insulin Receptor Substrate Proteins", "insulin resistance", "Insulin-Secreting Cells", "glycemic markers", "diabetes mellitus". The data terms were searched as mesh terms or abstract of studies.

Eligibility Criteria

In this systematic review, studies are considered by the assessment of the effect of CGA on insulin, GIP, and GLP-1 level. Inclusion criteria included:(1) studies conducted on the healthy human; (2) studies with complete data about the subject, method of study and characteristics of participants; (3) studies by randomized clinical trial design; 4) studies that have full text. Also, exclusion criteria included (1) studies without full-text; (2) studies without enough information about the subject, method of study and characteristics of participants 3) studies conducted on other than healthy humans; (4) studies with no randomized clinical trials design.

Data Extraction

We used the standard methods and detailed instruction manual for data extraction. Duplicated studies were excluded, after searching studies based on the literature search in databases. Then studies were sorted separately according to titles and abstracts by the searching about inclusion criteria and gained complete reports for all titles which looked to satisfy the inclusion criteria. In the next stage, studies sorted out the full-text reports and searched for additional information from studies to resolve the question about eligibility, where necessary. Data items were included demographic information, intervention detail such as dosage and trade name of the experimental intervention, duration of treatment, trial design, and trial sample size.

Method of Quality Assessment

The quality of studies was evaluated by the JADAD table which included the score of quality. This table included three items: randomization, blinding and dropouts in the study duration. The score of randomization and blinding is between zero and two that this depends on whether the method of randomization and blinding is clear descriptions or not. Also, the score of dropout is zero or one. Zero for studies with dropout and one for

studies by the lack of dropout. Anyway, JADAD scores are between zero for studies by low Quality and Five for studies by high quality (27).

Results

1631 articles were found and duplicate papers were omitted after the searching in databases. Then, 1564 papers remained which were classified based on relevance articles with the research title and having suitable abstract. So, 29 articles remained for the assessment of eligibility criteria, study design, presence or absence of the full-text and etc. In the final stage, due to the lack of eligibility criteria, 8 articles remained for qualitative synthesis and 21articles were omitted. Figure 1 shows search stages.

Quality Assessment

Based on the Jadad table, the qualitative assessment of studies showed that included studies were conducted randomly, but randomization method was explained in three of them. Also, seven papers were conducted by the blinding method, while this method was only explained in one of them (28-30). Finally, of 8 final papers, just three of them had dropouts while other studies participants had continued the study by the final stage. Johnston et al obtained the lowest score and Wedick et al had the highest score (14,30). The scores of Jadad table have been shown in Table 1.

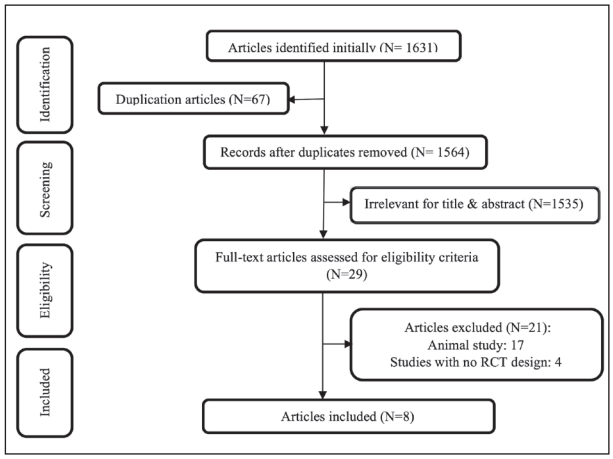

Figure 1: Flow chart of study selection

Study Characteristics

Overall, a total number of participants in all included studies were 136 individuals that all of them had the age range of 18-60. Men population (75%) were higher than the women (25%) in included studies. Studies were conducted in Japan (N=3) (31-33), China (N=1) (28) and USA (N=4) (14,29,30,34). Studies were published in the years 2003-2015. In the viewpoint of study design, 3 studies were conducted as randomized clinical trial by the parallel design and other studies were of the type cross over. Follow-up duration was between 2 hours to 6 hours in the conducted studies. Details of the studies are presented in Table 1.

CGA sources and isomers

Overall, four studies of included studies were used decaffeinated coffee (DCC) as one of the CGA groups, while other studies have used coffee polyphenol. Two studies were used GCA as intervention arms directly while one of the intervention arms was caffeinated coffee (CC) in Wedick et al (30). Also, four included studies were used the coffee bean as the source of CGA group, while other studies were used coffee granules as the source of it. CGA method extraction was hot water in three studies and other studies were not mentioned it. CGA isomers form tested were 3, 4, 5-caffeoylquinic acid; 3,4,5 feruloylquinic acid and 3,4/3,5/4,5 dicaffeoylquinic acid in the four studies while total isomers form tested were 3, 4, 5-caffeoylquinic acid among them. The isomers of CGA were measured by high-performance liquid chromatography from CGA sources in the studies cited. Table 1 show study characteristics.

Outcomes

One note for the analysis of data obtained from the review of studies entered into the qualitative synthesis shall be attended: some studies entered into the final stage of search have several intervention arms, so that each arm was considered as one independent intervention group for studying the final result. Table 1 show study characteristics.

Insulin: results of the studies entered into the final search stage showed that the level of blood insulin was not only measured in one study (28). Johnston et

Table 1: Characteristics of the studies included in the qualitative synthesis

study	Johnston (14)	Van Dijk (29)	Olthof (28)	Wedick (30)	Beam (34)	Ochiai (32)	Ochiai (31)	Jokura (33)
year	2003	2009	2011	2011	2015	2014	2015	2015
location	USA	USA	China	USA	USA	Japan	Japan	Japan
Target population	9 healthy subjects (4 male & 5 female)	15 healthy male	15 healthy male	41 healthy subjects (12male & 29female)	10 male cyclists	14 healthy male	13 healthy male	19 healthy male
Age (year)	22.8 – 29.2 Mean: 26	23.4 - 56.4 Mean: 39.9	23.4 - 56.4 Mean: 39.9	(27.5-53.7) Mean:40	21 – 31 Mean: 26	20 – 60 Mean: 40	30-60 Mean: 44.9	24 – 53 Mean: 38.1
BMI (kg/m2)	< 25	25 – 35	25 – 35	25 – 35	19.7-28.3	18.6– 26.5	NR	19.5– 24.1
Design	cross over	cross over	cross over	parallel	Parallel	cross over	cross over	parallel
Jadad score	2	3	3	5	3	3	3	3
Chlorogenic acid group	1) DCC + Glucose	1) DCC 2) CGA	1) DCC 2) CGA	1) DCC 2) CC	1) GCB + Dextrose	1) CPP + Glucose	1) CBPs	1) CPE
Chlorogenic acid dosage	1) 2.5 mmol	1) 264 mg 2) 1000 mg	1) 264 mg 2) 1000 mg	1) 264 mg 2) 302 mg	1) 350 mg	1) 600 mg	1) 600 mg	1) 355 mg
Chlorogenic acid total isomers	3-CQA , 4-CQA , 5-CQA	NR	NR	NR	NR	3,4,5 CQA 3,4,5 FQA 3,4/ 3,5 and 4,5-diCQA	3,4,5 CQA 3,4,5 FQA 3,4/ 3,5 and 4,5-diCQA	3,4,5 CQA 3,4,5 FQA 3,4/ 3,5 and 4,5-diCQA
Extraction method of isomers	HPLC	NR	NR	NR	NR	HPLC	HPLC	HPLC
Source and method of chlorogenic acid group extraction	coffee granules (no reported type of plant and method)	1) coffee granules (no reported type of plant and method) 2) NR	1) coffee granules (no reported type of plant and method) 2) NR	1&2) coffee (no reported type of plant and method)	green coffee bean (no reported method)	green coffee bean (hot water extraction method)	green coffee beans (hot water extraction method)	Roasted coffee beans (hot water extraction method)
Preparing method of intervention compounds	coffee were dissolved in 25 gr glucose into boiling water	Two supplements were dissolved in 270 mL of water	Two supplements were dissolved in 270 mL of water	Two supplements were dissolved in 177 mL of boiling water	GCB + 75 gr of dextrose mixed in 500 mL of water	CPP were used by 225 mL of a 75 gr Glucose - test solution	CBP beverage were dissolved in 100 mL of water	185 ml of CPE beverage were used directly
Control group	Glucose	Mannitol	Mannitol	Placebo beverage (No coffee)	Dextrose	Glucose	placebo beverage (No CBPs)	placebo beverage (No CPE)
Duration	180 min	120 min	120 min	120 min	120 min	120 min	360 min	240 min
Insulin (AUC)	No significant	1) No significant 2) No significant	NR	1) No significant 2) No significant	No significant	No significant	No significant	No significant
GIP (AUC)	lower significant	NR	1) No significant 2) No significant	NR	NR	No significant	NR	No significant
GLP-1 (AUC)	No significant	NR	1)No significant 2)No significant	NR	NR	No significant	NR	Higher significant

al demonstrated that consumption of DCC leads to the reduction in insulin concentration compared with control in the incremental AUC from 0 to 30 min (14). Also, we observed reduction in insulin level at 15 min after the start of experiment in CGA arm in Van Dijk et al only, and increase in insulin concentration with the use of CGA directly compared to baseline in Ochiai et al., but no significant effect of CGA on the level of blood insulin was observed in the each of studies, during total experimental period compared to control (29,32).

GIP: Overall, 4 studies have not been measured GIP while 4 studies were measured it as one of the outcomes. Johnston et al demonstrated that use of DCC leads to the reduction in GIP concentration compare with control (14), while the consumption of CGA in the form of coffee polyphenols led to significant increase in insulin level at 60 and 120 minutes of the Ochiai et al study duration, compared to baseline, but the intended intervention in this study had no effect on blood insulin compared to control (32).

GLP-1: Among all studies entered into the qualitative synthesis, 4 studies were measured GLP-1 as one of the outcomes. Jokura et al showed that CGA consumption increases level of GLP-1 (33). Also, the results of Johnson et al., and Olthof et al., showed that the consumption of CGA, in the form of DCC, led to increase the level of GLP-1 in the certain times of experimental period, but no significant effect on the level of this hormone was observed compared to the control, generally (14,28). GLP-1 concentration tended to be higher at 60 and 120 minutes of the Ochiai et al., duration compared to baseline but was not significant compare with control.

Discussion

Main Finding

Our finding showed that the consumption of CGA in the form of coffee extracts has no significant effect on insulin level while it was affected GIP (lowering effect) and GLP-1 (rising effect) in a few studies. So, several points may be contributing to these results:

Source of CGA groups was coffee granules in some included studies and others were used coffee polyphenol which can be included some polyphenols, such as DCC and CC. Given that the coffee is one of the main compounds extracted from the coffee bean, so it has different polyphenol compounds, and CGA is known as one of the functional substances (35, 36). Therefore, the effectiveness of CGA on insulin, GIP, and GLP-1 can be affected by other extract compounds and it can be caused a bias for studies included results. Also, as regards to the form of CGA in included studies (DCC, CC and coffee polyphenol extracts), assumptions listed above is honest related to CGA sources. One of the assumptions creates a challenge is the role of caffeine in impressment on included studies results. GIP was decreased in Johnston et al., due to the consumption of DCC, and coffee polyphenols-enriched CC could be increased GLP-1concentration in jokura et al. It is may be that CGA increased GLP-1 at low doses, in the form of CC, and causes the GIP reduction, in the form of DCC, at high doses in healthy humans. So, it has needed further studies. Table 1 show studies detail.

One of the important factors is the use of different CGA dosage in studies which may be affected results. As the evaluation of previous studies, there is no standard dosage of CGA for the affected insulin, GIP and GLP-1 in healthy humans. The range of CGA dosage was 355 to 1000 mg in included studies. GIP concentration was decreased in Johnston et al., due to the use of 2.5 mmol of CGA in DCC form by the coffee granules source, while GLP-1 was increased in Jokura et al., by the use of 355 mg of it in coffee polyphenol extract form with coffee bean source (14,33). However, other included studies were used the different dose of CGA, while they have obtained no significant effect on GIP, GLP-1, and insulin. This observation demonstrated that CGA by coffee granules source may be decreased GIP level, and CGA by coffee bean source may be increased GLP-1, but due to the low number of studies by human participants for this issue, the validity of this conclusion is poor and it have needed further studies.

Due to the assessment of preparing method of intervention compounds, Johnston et al., Beam et al., and Ochiai et al., had used glucose and dextrose in CGA groups. One of the mechanisms of CGA affected metabolism of the insulin, GIP and GLP-1 is the prohibiting of glucose absorption in the gut (14,16). So, the use

of glucose and dextrose can be affected insulin, GIP and GLP-1 with the synergistic effect of CGA.

The difference in sample size may be affected outcomes and which may be one of the reasons for reported different results in studies. Small sample size may have biased the study results (37). Johnston et al., and Jokura et al., with lowering effect in GIP level and increasing effect in GLP-1 concentration respectively, had 9 and 19 healthy subjects. Low sample size may be has affected the power of studies results.

Lack of the clear describing of randomization and allocation concealment approaches in most studies, compromises the interior validity of studies included qualitative synthesis, and subsequently limits the stability of conclusions that can be drawn on the effectiveness of CGA on GIP, GLP-1 and insulin (38).

Studies included qualitative synthesis had evaluated the acute effect of CGA on insulin, GIP, and GLP-1. Due to the lack of enough human studies about this subject, it is may be that CGA can affect these hormones in long duration and it have need added studies.

The total isomers of CGA which were used in some included studies were 3, 4, 5 caffeoylquinic acids (3, 4, 5 CQA), while there are four subtypes of CGA isomers included: caffeoylquinic acid, dicaffeoylquinic acids, feruloylquinic acids and p-coumaroylqunic acids. So, the range of the effect of each isomers on insulin, GIP, and GLP-1 may be different and led to different results.

Regarding that studies were conducted on healthy subjects in included studies, so there is a possibility to find different and opposite results for insulin, GIP, and GLP-1 concentration in other individuals, like diabetic patients compared to our findings, and subsequently more need is felt to conduct more exact clinical trials.

Due to the assessment of the previous animal studies, evidence showed similar results, compare with some included studies. For instance, the results of study conducted by Tunnicliffe et al., showed that the consumption of CGA has no effect on insulin and GLP-1 secretion in laboratory animals, but it can decrease the plasma response of GIP after eating, which is similar to Johnston et al., results (14,39). Overall, as regard to the lack of enough human studies, it is difficult to conclude the lowering effectiveness of CGA on GIP.

Limitations

Some studies were not reported outcome data completely which limited more comparisons of studies and performed meta-analysis on this issue. From the point of view of the qualitative assessment, one study acquire the highest score for describe method of randomization, blinding and dropouts while the other studies could not acquire the complete score of jadad items. Also, due to the assessment of included studies methods section, inadequate control for confounders may bias the results in the studies and affect our conclusions.

Conclusion

According to our findings in this systematic review, it was recognized that 1) the consumption of CGA in the form of DCC has lowering effect on GIP and has increasing effect on GLP-1 concentration in the form of coffee polyphenol extract in acute time, but this conclusion has low validity regards to low number of studies 2) consumption of CGA in the each form of coffee extract has no significant effect on the level of insulin. So, as regard to the lack of enough clinical human studies for this issue, so it is recommended to conduct further clinical trials in the future.

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