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A systematic review and meta-analysis on the efficacy and safety of traditional Chinese patent medicine Jinqi Jiangtang Tablet in the treatment of type 2 diabetes

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ABSTRACT

Introduction: At present, a large number of people in the world are suffering from type 2 diabetes (T2DM), so it is urgent to develop effective treatment measures of T2DM. In China, many clinical studies have shown that Jinqi Jiangtang Tablet (JQJTT), a traditional Chinese patent medicine (TCPM), has a good effect in the treatment of T2DM. This systematic review and meta-analysis is intended to assess the efficacy and safety of JQJTT plus conventional therapy in the treatment of T2DM.

Methods: Seven electronic databases were searched to include in eligible studies published from inception to May 24, 2018. Randomized controlled trials (RCTs) of JQJTT in combination with the conventional therapy versus conventional therapy alone or combined with placebo were included. The two reviewers independently conducted data extraction and quality assessment. For different variable types, the outcome measures were expressed as risk ratios (RRs) or mean differences (MDs). According to the value of I^2, a fixed or random effect model was used for statistical analysis.

Results: Seventeen studies conducted in China were identified in this systematic review, which included 1,425 participants. The meta-analysis on the effective rate of the comparison groups showed a significant difference in favor of the JQJTT group (RR 1.34; 95%CI [1.02, 1.75]; $p = 0.04$). In addition, the results showed a statistically significant reduction in FBG (MD −0.85; 95%CI [−1.03, −0.68]; $p < 0.00001$), 2hPG (MD −1.95; 95%CI [−2.33, −1.56]; $p < 0.00001$), HbA1c (MD −0.76; 95%CI [−1.03, −0.49]; $p < 0.00001$), FINS (MD −3.05; 95%CI [−3.69, −2.42]; $p < 0.00001$), PINS (MD −10.22; 95%CI [−13.93, −6.50]; $p < 0.00001$), HOMA-IR (MD −1.11; 95%CI [−1.55, −0.68]; $p < 0.00001$), LDL-C (MD −0.37; 95%CI [−0.63, −0.11]; $p = 0.006$), TC (MD −0.46; 95%CI [−0.85, −0.08]; $p = 0.02$), TG (MD −0.34; 95%CI [−0.47, −0.20]; $p < 0.00001$) with JQJTT plus conventional therapy versus conventional therapy alone. There was no statistical difference between the two comparison groups in HDL-C, total incidence of adverse events and incidence of hypoglycemia.

Conclusion: The available evidence indicates that JQJTT combined with conventional therapy for treating T2DM has a good performance in regulating glycolipid metabolism and improving insulin resistance. However, due to the limitations of this systematic review, the results should be interpreted with caution.

Incidents of diabetes mellitus (DM) are growing rapidly around the world, with the number of people suffering from the disease reaching 425 million, of whom 114 million are in China, accounting for 10.91% of Chinese adult population.[1] Type 2 diabetes mellitus(T2DM) is the most common form of DM, accounting for 90–95% of the whole diabetes population.[2] T2DM is characterized by chronic insulin resistance and insufficient insulin secretion,[3–5] which can lead to serious complications of macrovascular and microvascular complications, including cardiovascular diseases, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and so on.[6] Therefore, early treatment of T2DM and prevention of complications are highly important. However, the exact pathologic mechanism of T2DM has not been elucidated and may be related to many factors. Conventional drugs currently used to treat T2DM include Biguanides, α-Glucosidase inhibitors,

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Sulfonylureas, Thiazolidinediones, GLP-1 analogs, and DPP-4 inhibitors.

In China, T2DM is often treated in combination with Traditional Chinese Medicine (TCM) on the basis of its conventional therapy. TCM has been used widely to treat diseases in China for thousands of years, and traditional Chinese patent medicine (TCPM) is developed by combining TCM theories with modern biotechnology and pharmacological technology, which is more convenient for clinical use.[7] Approved by the State Food and Drug Administration of China (state medical license number ZYB20720041440), Jinqi Jiangtang tablet (JQJTT) is a TCPM for the treatment of T2DM. It consists of Radix Astragali (Huang Qi), Rhizoma Coptidis (Huang Lian), lonicera japonica (Jin Yin Hua), which has the function of clearing heat and fortifying qi (vital energy). At present, the study on the mechanism of this medicine has shown that it works by improving glycolipid metabolism, insulin resistance and enhancing immune function.[8] In clinical practice, JQJTT has been used in the treatment of T2DM in China for many years, and a number of published clinical studies conducted in China have suggested that it is effective in treating T2DM, but there lacks systematic evidence of the effect. Therefore, this systematic review and meta-analysis was performed to assess the efficacy and safety of JQJTT plus conventional therapy in the treatment of T2DM.

1. Methods

1.1. Protocol and registration

This review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42018104732; available online at http://www.crd.york.ac.uk/PROSPERO/myprospero.php). It was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

1.2. Selection criteria

All studies included in the systematic review should meet the following criteria: (1) the studies included participants diagnosed with T2DM by clearly defined or internationally recognized criteria, regardless of gender, age and ethnicity; (2) the intervention group was treated with JQJTT combined with conventional therapy, and the control group was treated with conventional therapy alone or combined with placebo; (3) the studies were randomized controlled trials (RCTs); and (4) the studies were published either in Chinese or English. At the same time, some studies would be excluded if the intervention group or control group were combined with other TCM therapies (other TCPM, acupuncture, herbal formulas) except JQJTT.

1.3. Information sources and search

The following seven electronic databases were searched for relevant literature from inception to 24 may 2018: the Cochrane Library, PubMed, Embase, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, Chinese scientific Journal Database (VIP) and the Wanfang database. At present, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, Chinese scientific Journal Database (VIP) and the Wanfang database are the recognized medical research databases in mainland China, covering almost all the published medical research articles in China. As JQJTT is a TCPM, it is mainly used in China. In order to obtain the maximum possible number of clinical studies, the retrieval of four Chinese electronic databases was conducted.

The following items(either as key words or Mesh terms) were used individually or in combination to retrieve 7 electronic databases for related literature published in English or Chinese:(“randomized controlled trial” OR RCT)AND(“Diabetes Mellitus, Type 2” OR “Type 2 Diabetes” OR “Diabetes, Type 2” OR “Type 2 Diabetes Mellitus” OR “Diabetes Mellitus, Noninsulin-Dependent” OR “Diabetes Mellitus, Ketosis-Resistant” OR “Diabetes Mellitus, Ketosis Resistant” OR “Ketosis-Resistant Diabetes Mellitus” OR “Diabetes Mellitus, Non Insulin Dependent” OR “Diabetes Mellitus, Non-Insulin-Dependent” OR “Non-Insulin-Dependent Diabetes Mellitus” OR “Diabetes Mellitus, Stable” OR “Stable Diabetes Mellitus” OR “Diabetes Mellitus, Type II” OR “NIDDM” OR “Diabetes Mellitus, Noninsulin Dependent” OR “Diabetes Mellitus, Maturity-Onset” OR “Diabetes Mellitus, Maturity Onset” OR “Maturity-Onset Diabetes Mellitus” OR “Maturity Onset Diabetes Mellitus” OR “MODY” OR “Diabetes Mellitus, Slow-Onset” OR “Diabetes Mellitus, Slow Onset” OR “Slow-Onset Diabetes Mellitus” OR “Noninsulin-Dependent Diabetes Mellitus” OR “Noninsulin Dependent Diabetes Mellitus” OR “Maturity-Onset Diabetes” OR “Diabetes, Maturity-Onset” OR “Maturity Onset Diabetes” OR “Diabetes Mellitus, Adult-Onset” OR “Adult-Onset Diabetes Mellitus” OR “Diabetes Mellitus, Adult Onset”) AND (“Jinqi Jiangtang”).

In addition, to include unpublished studies, we also searched the website of the international clinical trial registry provided by the U.S. National Institutes of Health (available at http://ClinicalTrials.gov/) and the Chinese Clinical Trial Registry (available at http://www.chictr.org.cn/index.aspx). In order to include the eligible studies as fully as possible, the reference lists of relevant retrieved studies were manually searched, too.

1.4. Study selection

The two reviewers independently read the titles and abstracts for preliminary screening. Then the full texts were further examined to determine the eligible studies that were eventually included in the system review. Any discrepancies were resolved by consensus or after consulting a third party.

1.5. Data extraction

Two reviewers independently extracted and collected data from the included studies using a pre-designed data collection form as follows: general trial characteristics (title, authors, year); baseline data including patients and diseases information (sample size, age, gender, diagnostic criteria, course of the disease); interventions (dosage of traditional Chinese patent medicine, details of the control interventions, intervention period); outcomes (outcome measures, adverse events). Discrepancies were settled by consensus, or consultation with a third party.

1.6. Outcome measures

This system review reported both primary and secondary outcomes. The primary outcomes included effective rate (effective rate (%) = number of effective cases/total number × 100%), fasting blood glucose (FBG, mmol/L), two-hour postprandial blood glucose (2h PG, mmol/L), and glycosylated hemoglobin (HbA1C, %). The secondary outcomes included the total incidence of adverse events (%), incidence of hypoglycemia (%), fasting insulin (FINS, mIU/L), postprandial insulin (PINS, mIU/L), HOMA-IR, high density lipoprotein cholesterol (HDL-C, mmol/L), low density lipoprotein cholesterol (LDL-C, mmol/L), Triglyceride (TG, mmol/L), total cholesterol (TC, mmol/L).

Refer to the relevant standards of type 2 diabetes in Guiding principles for clinical research of new Chinese medicine, the marked effective criteria is that FBG, 2hPG and HbA1c decrease to normal range or FBG and 2hPG decrease by more than 40% or HbA1c decreases by more than 30%. The effective criteria is a 20% or more reduction in FBG or 2hPG level and a 10% or more reduction in HbA1c level, but does not meet the marked effective criteria. Refer to the relevant standards of hyperlipemia in Guiding principles for clinical research of new Chinese medicine, the marked effective criteria is that TC

decreases by more than 20% or TG decreases by more than 40% or HDL-C increases by more than 0.26 mmol/L (10 mg/dl) or TC-HDL-C/HDL-C decreases by more than 20%. The effective criteria is TC decreases by more than 10% but less than 20% or TG decreases by more than 20% but less than 40% or HDL-C increases by more than 0.104 mmol/L (4 mg/dl) but less than 0.26 mmol/L (10 mg/dl), or TC-HDL-C/HDL-C decreases by more than 10% but less than 20%.

1.7. Quality assessment

Two reviewers independently used the risk of bias tool recommended by the Cochrane Collaboration to assess the methodological quality of the included studies. The risk of bias assessment was performed according to the method in Cochrane Handbook,[9] which was consisted of six items: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other sources of bias. Each item was categorized as "high risk" (at least one item has a high risk of bias), "low risk" (all items have a low risk of bias), "unclear" (at least one item has an unclear risk of bias). Other biases included profit bias and the sample calculation. Discrepancies in the interpretation were resolved by consensus, or consultation with a third party

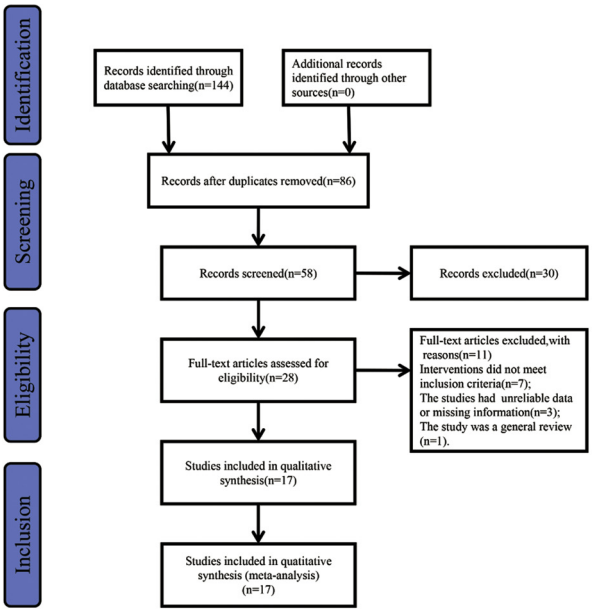
1.8. Statistical analysis

The data were analyzed using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). We used I^2 statistics to evaluate the statistical heterogeneity across studies. If there was no significant heterogeneity between studies ($I^2 < 50\%$), the fixed-effects (FE) model would be used, and if there was significant heterogeneity between studies ($I^2 > 50\%$), a random-effects (RE) model would be used.[10] For dichotomous outcomes, risk ratios (RRs) were used as the effect measures by the Mantel-Haenszel method, and for continuous variables, weighted mean differences (MDs) were used as the effect measures by the inverse variance method. For all estimates, we computed 95% confidence intervals (CIs). A sensitivity analysis was carried out to assess the robustness of the results of the meta-analysis in terms of the primary outcomes. Subgroup analyses were conducted with treatment duration, sample size, the kind of conventional therapy to observe whether the results changed. When more than 10 studies were included, publication bias was evaluated by funnel plot analysis.

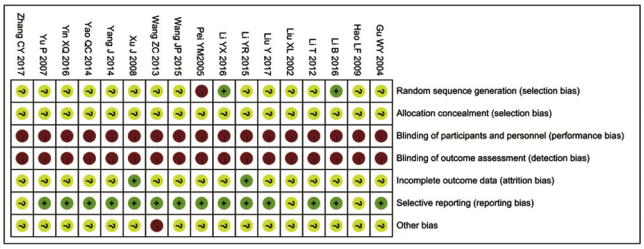
2. Results

2.1. Study selection

After searching, 144 identified studies were selected. 86 duplicate articles were deleted. And the remaining 58 studies entered the preliminary screening stage, in which 30 articles were excluded by reading titles and abstracts. The specific reasons for exclusion were as follows: (1) 2 studies were systematic review and meta-analysis; (2) 2 studies were animal experiments; (3) 4 studies were non-randomized controlled trials; (4) 5 studies were on pre-diabetes; (5) 5 studies were on diabetes complications; (6) In 10 studies, the intervention measures of the control group were Chinese herbal compound or TCPM; (7) 2 studies were not relevant. Then 28 studies needed to be determined whether they should be included in the systematic review by reading the full text. In the process of full text reading, 11 studies were excluded for the following reasons: (1) interventions in 7 studies did not meet the inclusion criteria; (2) 3 studies had unreliable data or missing information; (3) 1 study was a general review. Eventually, 17 studies[11–27] which were performed in China were eligible for this systematic review, and the PRISMA flow diagram is shown in Fig. 1A.



A PRISMA flow diagram of literature



B Risk bias of graph

Fig. 1. PRISMA flow diagram and Risk bias of graph.

2.2. Study characteristics

The basic characteristics of the included studies are shown in Table 1. A total of 1425 participants were involved, all of whom were Chinese subjects, 723 in the treatment group and 702 in the control group. All participants in included studies were from inpatients or outpatients. The sample size for all studies ranged from 30 to 158, 776 males and 649 females. All participants in included studies were diagnosed with T2DM, and 15[11,13,15–27] of these studies provided clear diagnostic criteria of T2DM, which were the WHO diagnostic criteria or other internationally recognized diagnostic criteria. Li T 2012[19] mentioned that the syndrome of TCM was dual deficiency of qi-yin, while the remaining studies did not put forward the classification of TCM syndromes according to TCM theory. All included studies compared JQJTT plus conventional therapy with the conventional therapy alone and the specific drugs for conventional therapy in each of the original study were shown in Table 1. Tianjin zhongxin pharmaceutical group co., LTD. Longshunrong pharmaceutical factory was the only manufacturer of JQJTT approved by China Food and Drug administration. In this systematic review, 13 studies[11–13,15–20,22,24,26,27] clearly proposed that JQJTT was produced by Tianjin zhongxin pharmaceutical group co., LTD. Longshunrong pharmaceutical factory, while other 3 studies[14,23,25] did not indicate the manufacturer of JQJTT. Liu XL 2002[21] indicated that JQJTT was produced by tianjin traditional Chinese medicine factory. All included studies were conducted in China and the treatment duration lasted from 20 days to 6 months. In the primary outcomes, five studies[11,16–18,26] reported effective rate, and only Li B

Table 1
Characteristics of the included studies.

First anthor,year	Sample size, SEX:M/F	Age (years)	Course of diabetes(years)	Diagnostic criteria	Syndrome of TCM	Intervention		Intervention period	Outcome measure	Adverse events	Follow up
						Treatment group (T) Manufacturer	Control group (C)				
Zhang CY 2017 [12]	T:30(17/13) C:30(18/12)	T:(55.43 ± 7.12) C:(56.13 ± 6.95)	T:(6.39 ± 3.24) C:(6.13 ± 2.89)	NR	NR	JQTT (7 tablet, 0.56g/tablet, tid) +control LSR pharmaceutical factory	Metformin(0.5~2.0g, tid)	NR	①HbA1c②2hPG	NR	NR
Yang J 2014 [14]	T:35, C:35 M/F:39/31	(42.56±10.32)	Not report	NR	NR	JQTT(7~10 tablet, tid)+control NR	Pioglitazone(30mg, qd)	6 months	①FBG②FINS③2hPG ④PINS	T:3 C:4	NR
Wang JP 2015 [15]	T:50(28/22) C:50(27/23)	T:(65.0±2.4) C:(64.3±2.3)	Not report	1999 WHO	NR	JQTT(2~3 tablet,0.42g/tablet, tid) +control LSR pharmaceutical factory	Pioglitazone(15~50mg, qd)	2 months	①FBG②2hPG ③HbA1c	NR	NR
Pei YM 2005 [24]	T:42(22/20) C:38(18/20)	T:(47.9±8.7) C:(49.2±9.8)	T:(11.7 ± 6.2) C:(12.7 ± 7.1)	1999 WHO	NR	JQTT(6~12 tablet, 0.56g/tablet, tid)+control LSR pharmaceutical factory	Pioglitazone(15mg,qd or bid)	12 weeks	①FBG②2hPG ③HOMA-IR	NR	NR
Liu XL 2002 [21]	T:26, C:26 M/F:34/18	57.5±6.6	6.8±3.6	1999 WHO	NR	JQTT (7 tablet, tid)+control Tianjin traditional Chinese medicine factory	Metformin(750~1500 mg/d)	8 weeks	①FBG②FINS	NR	NR
Wang ZC 2013 [27]	T:34(16/18) C:34(17/17)	T:(57.4±6.6) C:(57.7±6.9)	T:(6.9±3.7) C:(7.0±3.5)	1999 WHO	NR	JQTT(7~10 tablet, 0.56g/tablet, tid)+control LSR pharmaceutical factory	Pioglitazone(30mg, qd)	6 months	①FBG②2hPG③HOMA-IR ④FINS⑤PINS⑥HbA1c ⑦TC⑧TG	T:0 C:2(Mild edema)	NR
Yin XQ 2016 [22]	T:56(32/24) C:56(30/26)	T:(58.27±6.27) C:(58.15±6.09)	T:(6.27± 1.38) C:(6.13± 1.27)	1999 WHO	NR	JQTT(2~3 tablet, 0.42g/tablet, tid)+control LSR pharmaceutical factory	Pioglitazone(30mg, qd)	6 months	①FBG②2hPG③HbA1c ④FINS⑤PINS⑥HOMA-IR	NR	NR
Li YX 2016 [26]	T:38, C:38 M/F:36/40	51.8±3.6	7.5±1.3	1999 WHO	NR	JQTT (7 tablet, 0.56g/tablet, tid)+control LSR pharmaceutical factory	Metformin(0.5~2.0g, tid)	4 weeks	①effective rate②2hPG ③HbA1c④FBG	NR	NR
Yao QC 2014 [18]	T:34(18/16) C:34(17/17)	T:(54.5±6.9) C:(55.5±6.1)	T:(6.4±4.7) C:(7.6±3.5)	1999 WHO+ GFCRONCM	NR	JQTT (7 tablet, 0.56g/tablet, tid)+control LSR pharmaceutical factory	Metformin(0.5~2.0g, tid)	8 weeks	①effective rate②2hPG ③HbA1c④FBG⑤TC⑥TG ⑦LDL-C⑧HDL-C	T:0 C:0	NR
Yu P 2007 [17]	T:33(15/18) C:32(17/15)	T:65.5 C:64.1	Not report	1999 WHO	NR	JQTT(6~10 tablet, 0.56g/tablet tid)+control LSR pharmaceutical factory	Glipizide(5~15mg, qd)	12 weeks	①effective rate②2hPG ③HbA1c④FBG⑤FINS ⑥TG⑦TC	T:0 C:0	NR
Li T 2012 [19]	T:50(28/22) C:50(26/24)	T:(46.5±6.3) C:(43.8±4.7)	T:2~20 C:2~24	1999 WHO+ GFCRONCM	Deficiency of qi and Yin	JQTT(7~10tablet,0.56g/tablet, tid)+control LSR pharmaceutical factory	Glimepiride(2mg, bid)+ Metformin(1g, bid)	12 weeks	①2hPG②HbA1c③FBG ④TG⑤TC⑥LDL-C	NR	NR
Gu WY 2004 [20]	T:80(42/38) C:78(47/31)	T:55.6 C:53.7	Not report	1998 ADA	NR	JQTT(30 tablet/d, 0.56g/tablet) +control LSR pharmaceutical factory	Gliclazide(160~240mg/d, bid or tid)	12 weeks	①FBG②FINS③HbA1C ④TG⑤TC⑥HDL-C ⑦LDL-C	T:1(Mild hypoglycemia) C:5(Mild hypoglycemia)	NR
Hao LF 2009 [16]	T:52(26/26) C:51(29/22)	T:(53.31± 7.25) C:(52.57± 7.83)	T:(3.77± 3.07) C:(4.09± 2.98)	GFCRONCM	NR	JQTT(8~10 tablet, 0.56g/tablet, tid)+control LSR pharmaceutical factory	Metformin(0.25~0.5g, tid)+ acarbose(50mg, tid)	30 days	①FBG②2hPG③TC ④TG⑤HDL-C	T:0 C:0	NR
Li YR 2015 [25]	T:15(10/5) C:15(7/8)	T:(53.97±8.32) C:(54.01±7.14)	Not report	1999 WHO	NR	JQTT(0.56g, tid)+control NR	Saxagliptin(2.5mg, tid)	20 days	①FBG②2hPG	T:0 C:0	NR
Li B 2016 [11]	T:35(18/17) C:35(19/16)	T:(52.65±6.39) C:(52.71±6.44)	Not report	1999 WHO	NR	JQTT(1 tablet, 0.56g/tablet, tid)+control LSR pharmaceutical factory	Saxagliptin(2.5mg, tid)	20 days	①FBG②2hPG③effective rate	T:1(Mild diarrhea) C:0	NR
Xu J 2008 [13]	T:33(20/13) C:30(19/11)	T:(58.4±7.7) C:(56.6±8.9)	Not report	1999 WHO	NR	JQTT(8 tablet, 0.56g/tablet, tid)+control LSR pharmaceutical factory	(Biguanides+Sulfonylureas) or (Biguanides+acarbose)	3 months	①FBG②2hPG③HbA1c④TC ⑤TG⑥HDL-C⑦LDL-C	NR	NR
Liu Y 2017 [23]	T:80, C:70 M/F:(84/66)	48.4±8.1	4.6±2.8	1999 WHO	NR	JQTT (7 tablet, tid)+control NR	Metformin≤2000mg/d	12 weeks	①FBG②2hPG③HbA1c④TC ⑤TG⑥HDL-C⑦LDL-C	NR	NR

GFCRONCM, guidelines for clinical research of new Chinese medicine; NR, not report; LSR pharmaceutical factory, Tianjin zhongxin pharmaceutical group co., LTD. Longshunrong pharmaceutical factory.

2016[11] fully met the effective criteria of guiding principles for clinical research of new Chinese medicine. Effective criteria of Yao QC 2014[18] included a 10–30% reduction in 2hPG. Effective criteria in other 4 studies[11,16,17,26] included a reduction of more than 20% in 2hPG. We found that the effective criteria for the five studies[11,16–18,26] were similar, and all of them were close to the effective criteria of guiding principles for clinical research of new Chinese medicine. Sixteen studies[11,13–27] reported FBG, fifteen studies[11–19,22–27] reported 2h PG, and eleven studies[12,13,15,17–20,22,23,26,27] reported HbA1c. In the secondary outcomes, six studies[14,17,20–22,27] reported FINS, three studies reported PINS[14,22,27] and HOMA-IR,[22,24,27] five studies reported HDL-C[13,16,18,20,23] and LDL-C,[13,18,19,20,23] and eight studies[13,16–20,23,27] reported TC and TG. In terms of safety, eight studies[11,14,16–18,20,25,27] reported adverse events, including hypoglycemia, liver and kidney impairment, and other adverse events.

2.3. Methodological quality assessment

The risk of bias summary graph regarding each risk of bias item in the included trials is shown in Fig. 1B. Two trials[11,26] reported random sequence generation through a random number table, whereas the other trials reported "randomly allocating", but the detailed method of randomization were not provided. No trials gave detailed information about allocation concealment. Seventeen studies[11–27] were at high risk bias regarding blinding of participants and personnel and blinding of outcome assessment because the control group did not use a placebo. All included trials provided complete baseline information and described similarities between groups compared. Two trials[13,25] reported dropouts or withdrawals. Fourteen trials[11,13–15,17–20,22–27] were at low risk bias of selective reporting due to the reported expected outcome indicators. Wang ZC 2013[27] was at high risk bias on the level of other bias because one of the author's units of this study belonged to the pharmaceutical companies of JQJTT.

3. Primary outcomes

3.1. Effective rate

The forest map of effective rate is shown in Fig. 2A.1. Five trials[11,16–18,26] reported effective rate as an outcome. The heterogeneity across trials was significant (I^2 = 86%), thus a random-effects model was used for statistical analysis. The results of meta-analysis showed a better performance in the overall risk ratio of effective rate in favor of the JQJTT plus conventional therapy group (n = 382, RR 1.34; 95%CI [1.02, 1.75]; p = 0.04).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 2A.2). By excluding the original studies item by item, the results showed that when Li B 2016,[10] Li YX 2016,[25] Yu P 2007[16] were removed item by item from the meta-analysis, the conclusion of the meta-analysis changed, which indicated that the results were not stable in effective rate level.

3.2. Fasting blood glucose (FBG)

The forest map of FBG is shown in Fig. 2B.1. Sixteen trials[11,13–27] used FPG as an outcome. The heterogeneity across trials was significant (I^2 = 75%), therefore, a random-effects model was used for statistical analysis. The results of the meta-analysis revealed a statistically significant reduction in FBG level in JQJTT plus conventional therapy group compared to controls (n = 1365, MD −0.85; 95%CI [−1.03, −0.68]; p < 0.00001).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 2B.2). By excluding the original studies item by item from the meta-analysis, the heterogeneity across studies was still significant and the results showed that there was no change in the conclusion of the meta-analysis, which indicated that the results were stable.

3.3. 2h postprandial blood glucose (2h PG)

The forest map of 2h PG is shown in Fig. 2.C.1. In fifteen trials,[11–19,22–27] 2h PG were compared between the JQJTT plus conventional therapy group and conventional therapy group. The heterogeneity across trials was significant (I^2 = 77%), so a random-effects model was used for statistical analysis. The results of the meta-analysis showed a statistically significant difference in 2h PG level in favor of JQJTT plus conventional therapy group (n = 1215, MD −1.95; 95%CI [−2.33, −1.56]; p < 0.00001).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 2C.2). By excluding the original studies item by item from the meta-analysis, the heterogeneity across studies was still significant and the results showed that there was no change in the conclusion of the meta-analysis, which indicated that the results were stable.

3.4. Glycosylated hemoglobin (HbA1c)

The forest map of HbA1c is shown in Fig. 2D.1. Eleven trials[12,13,15,17–20,22,23,26,27] enrolling 1020 subjects used HbA1c as an outcome. The heterogeneity across trials was significant (I^2 = 80%), so a random-effects model was used for statistical analysis. The results of the meta-analysis showed a statistically significant reduction in HbA1c level in JQJTT plus conventional therapy than the conventional therapy alone (n = 1020, MD −0.76; 95%CI [−1.03, −0.49]; p < 0.00001).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 2D.2). By excluding the original studies item by item from the meta-analysis, and the heterogeneity across studies decreased after the removal of the study of Li YX 2016[25] (I^2 = 45%). Therefore, the study of Li YX 2016[25] might cause the heterogeneity of this outcome measure (i.e., HbA1c). However, after excluding this study, there was no change in the conclusion of the meta-analysis (MD −0.59; 95%CI [−0.75, −0.43]; p < 0.00001), which indicated that the results were stable.

4. Secondary outcomes

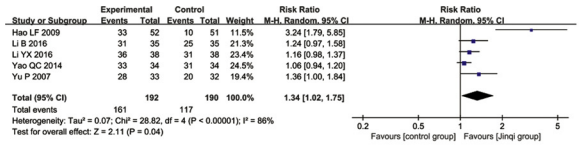
4.1. Fasting insulin (FINS)

The meta-analysis result in FINS level is shown in Fig. 3A. Six trials[14,17,20–22,27] enrolling 525 subjects used FINS as an outcome. The heterogeneity across trials was insignificant (I^2 = 10%); so a fixed-effects model was used for statistical analysis. A meta-analysis showed that there was a statistically significant reduction in FINS level in favor of JQJTT plus conventional therapy group (n = 525, MD −3.05; 95%CI [−3.69, −2.42]; p < 0.00001).

4.2. Postprandial insulin (PINS)

The meta-analysis result in PINS level is shown in Fig. 3B.1. Three trials[14,22,27] enrolling 250 subjects used PINS as an outcome. The heterogeneity across trials was significant (I^2 = 85%), so a random-effects model was used for statistical analysis. A meta-analysis showed that there was a statistically significant reduction in PINS level in favor of JQJTT plus conventional therapy group (n = 250, MD −10.22; 95%CI [−13.93, −6.50]; p < 0.00001).

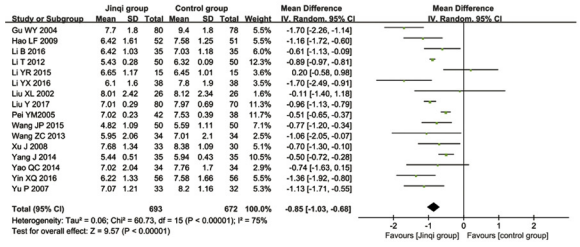
In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 3B.2). By excluding the original studies item by item from the meta-analysis, the heterogeneity across studies was still significant and the results showed that there was no change in the conclusion of the meta-analysis, which indicated that the results were stable.



A.1 Forest map of effective rate

Delete study	RR	95%CI	I^2	P(effect)
Hao LF 2009	1.15	[1.03,1.29]	28%	0.01
Li B 2016	1.4	[0.97,2.02]	91%	0.07
Li YX 2016	1.45	[0.95,2.23]	91%	0.09
Yao QC 2014	1.45	[1.04,2.02]	82%	0.03
Yu P 2007	1.35	[0.97,1.88]	90%	0.08

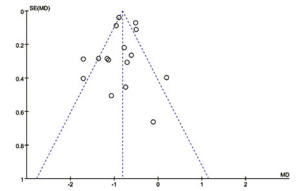
A.2 Sensitivity analysis of effective rate



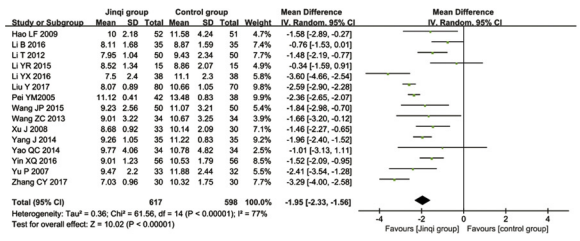
B.1 Forest map of FBG

Delete study	MD	95% CI	I^2	P(effect)
Gu WY 2004	-0.8	[-0.97,-0.63]	73%	<0.00001
Hao LF 2009	-0.83	[-1.02,-0.65]	76%	<0.00001
Li B 2016	-0.87	[-1.05,-0.69]	77%	<0.00001
Li T 2012	-0.86	[-1.07,-0.64]	74%	<0.00001
Li YR 2015	-0.89	[-1.06,-0.72]	74%	<0.00001
Li YX 2016	-0.82	[-0.99,-0.65]	75%	<0.00001
Liu XL 2002	-0.86	[-1.04,-0.69]	77%	<0.00001
Liu Y 2017	-0.84	[-1.04,-0.65]	76%	<0.00001
Pei YM 2005	-0.9	[-1.07,-0.72]	65%	<0.00001
Wang JP 2015	-0.86	[-1.05,-0.68]	77%	<0.00001
Wang ZC 2013	-0.85	[-1.03,-0.67]	77%	<0.00001
Xu J 2008	-0.86	[-1.04,-0.68]	77%	<0.00001
Yang J 2014	-0.89	[-1.08,-0.71]	73%	<0.00001
Yao QC 2014	-0.86	[-1.04,-0.68]	77%	<0.00001
Yin XQ 2016	-0.82	[-1.00,-0.64]	75%	<0.00001
Yu P 2007	-0.84	[-1.02,-0.66]	76%	<0.00001

B.2 Sensitivity analysis of FBG



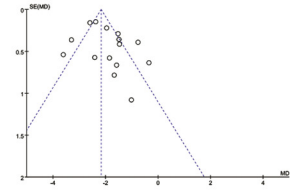
B.3 Funnel plot of FBG



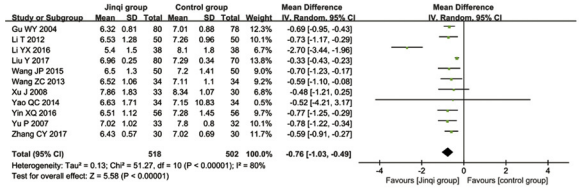
C.1 Forest map of 2h PG

Delete study	MD	95% CI	I^2	P(effect)
Hao LF 2009	-2.18	[-2.33,-2.02]	79%	<0.00001
Li B 2016	-2.23	[-2.39,-2.07]	73%	<0.00001
Li T 2012	-2.2	[-2.36,-2.05]	77%	<0.00001
Li YR 2015	-2.2	[-2.35,-2.04]	76%	<0.00001
Li YX 2016	-2.14	[-2.29,-1.98]	76%	<0.00001
Liu Y 2017	-2.03	[-2.21,-1.86]	75%	<0.00001
Pei YM 2005	-2.09	[-2.28,-1.91]	78%	<0.00001
Wang JP 2015	-2.18	[-2.33,-2.02]	79%	<0.00001
Wang ZC 2013	-2.17	[-2.33,-2.02]	79%	<0.00001
Xu J 2008	-2.2	[-2.35,-2.04]	78%	<0.00001
Yang J 2014	-2.2	[-2.36,-2.03]	79%	<0.00001
Yao QC 2014	-2.18	[-2.33,-2.02]	78%	<0.00001
Yin XQ 2016	-2.22	[-2.38,-2.06]	77%	<0.00001
Yu P 2007	-2.16	[-2.32,-2.01]	79%	<0.00001
Zhang CY 2017	-2.11	[-2.27,-1.96]	75%	<0.00001

C.2 Sensitivity analysis of 2h PG



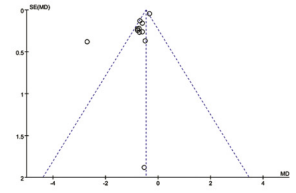
C.3 Funnel plot of 2h PG



D.1 Forest map of HbA1c

Delete study	MD	95% CI	I^2	P(effect)
Gu WY 2004	-0.78	[-1.09,-0.47]	81%	<0.00001
Li T 2012	-0.77	[-1.06,-0.48]	82%	<0.00001
Li YX 2016	-0.59	[-0.75,-0.43]	45%	<0.00001
Liu Y 2017	-0.83	[-1.11,-0.55]	68%	<0.00001
Wang JP 2015	-0.77	[-1.06,-0.48]	82%	<0.00001
Wang ZC 2013	-0.78	[-1.07,-0.49]	82%	<0.00001
Xu J 2008	-0.78	[-1.07,-0.50]	82%	<0.00001
Yao QC 2014	-0.76	[-1.03,-0.49]	82%	<0.00001
Yin XQ 2016	-0.76	[-1.05,-0.47]	82%	<0.00001
Yu P 2007	-0.76	[-1.05,-0.47]	82%	<0.00001
Zhang CY 2017	-0.79	[-1.10,-0.49]	82%	<0.00001

D.2 Sensitivity analysis of HbA1c



D.3 Funnel plot of HbA1c

Fig. 2. Primary outcomes comparison between JQJTT plus conventional therapy group and conventional therapy group.

4.3. HOMA-IR

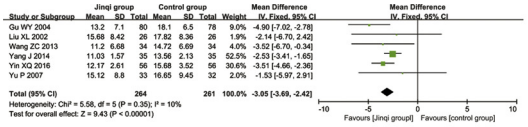
The meta-analysis result in HOMA-IR level is shown in Fig. 3C.1. Three trials[22,24,27] enrolling 260 subjects used HOMA-IR as an outcome. The heterogeneity across trials was significant (I^2 = 74%), so a random-effects model was used for statistical analysis. A meta-analysis showed that JQJTT plus conventional therapy had a statistically significant improvement in HOMA-IR level compared to the conventional therapy alone (n = 260, MD −1.11; 95%CI [−1.55, −0.68]; p < 0.00001).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 3C.2). By excluding the original studies item by item from the meta-analysis, and the heterogeneity across studies decreased significantly after the removal of the study of Pei YM 2005[23] (I^2 = 0%). Therefore, the study of Pei YM 2005[23] might cause the heterogeneity of this outcome measure (i.e., HOMA-IR). However, after excluding this study, there was no change in the conclusion of the meta-analysis(MD −1.34; 95%CI [−1.70, −0.97]; p < 0.00001), which indicated that the results were stable.

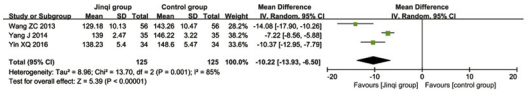
4.4. HDL-C

The meta-analysis result in HDL-C level is shown in Fig. 3D.1. Five trials[13,16,18,20,23] enrolling 542 subjects used HDL-C as an outcome. The heterogeneity across trials was significant (I^2 = 86%), so a random-effects model was used for statistical analysis. A meta-analysis showed no statistical difference in HDL-C level with JQJTT plus conventional therapy versus the conventional therapy alone (n = 542, MD 0.09; 95%CI [−0.07, 0.24]; p = 0.29).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 3D.2). By excluding the original studies item by item from the meta-analysis, the heterogeneity across studies was still significant and the results showed that there was no change in the conclusion of the meta-analysis, which indicated that the results were stable.



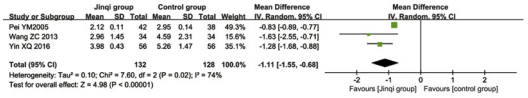
A Forest map of FINS



B.1 Forest map of PINS

Delete study	MD	95% CI	I^2	P(effect)
Wang ZC 2013	-8.59	[-11.66, -5.53]	78%	<0.00001
Yang J 2014	-11.95	[-15.54, -8.35]	60%	<0.00001
Yin XQ 2016	-10.41	[-17.11,-3.70]	91%	0.002

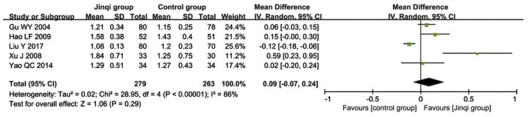
B.2 Sensitivity analysis of PINS



C.1 Forest map of HOMA-IR

Delete study	MD	95% CI	I^2	P(effect)
Pei YM 2005	-1.34	[-1.70, -0.97]	0%	<0.00001
Wang ZC 2013	-1.01	[-1.44, -0.58]	79%	<0.00001
Yin XQ 2016	-1.09	[-1.83, -0.36]	66%	0.004

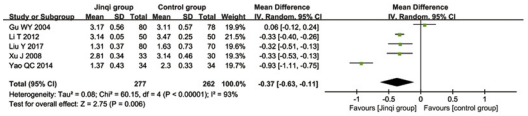
C.2 Sensitivity analysis of HOMA-IR



D.1 Forest map of HDL-C

Delete study	MD	95% CI	I^2	P(effect)
Gu WY 2004	0.11	[-0.12, 0.35]	88%	0.34
Hao LF 2009	0.07	[-0.11, 0.25]	87%	0.46
Liu Y 2017	0.14	[-0.01, 0.30]	65%	0.060
Xu J 2008	0.02	[-0.12, 0.16]	83%	0.79
Yao QC 2014	0.10	[-0.08, 0.29]	90%	0.27

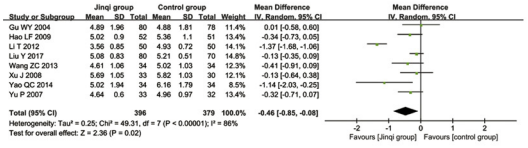
D.2 Sensitivity analysis of HDL-C



E.1 Forest map of LDL-C

Delete study	MD	95% CI	I^2	P(effect)
Gu WY 2004	-0.47	[-0.74, -0.21]	92%	0.001
Li T 2012	-0.38	[-0.80, 0.04]	95%	0.07
Liu Y 2017	-0.38	[-0.71, -0.05]	95%	0.02
Xu J 2008	-0.38	[-0.70, -0.05]	95%	0.02
Yao QC 2014	-0.23	[-0.41, -0.06]	82%	0.01

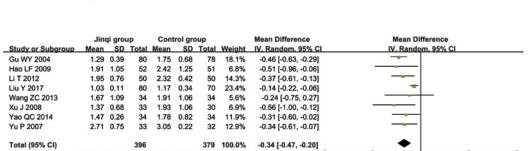
E.2 Sensitivity analysis of LDL-C



F.1 Forest map of TC

Delete study	MD	95% CI	I^2	P(effect)
Gu WY 2004	-0.52	[-0.94, -0.11]	0.9	0.01
Hao LF 2009	-0.48	[-0.93, -0.04]	0.9	0.03
Li T 2012	-0.24	[-0.40, -0.08]	0.1	0.003
Liu Y 2017	-0.52	[-0.96, -0.08]	0.8	0.02
Wang ZC 2013	-0.47	[-0.90, -0.04]	0.9	0.03
Xu J 2008	-0.51	[-0.93, -0.08]	0.9	0.02
Yao QC 2014	-0.4	[-0.80, 0.00]	0.9	0.05
Yu P 2007	-0.49	[-0.93, -0.04]	0.9	0.03

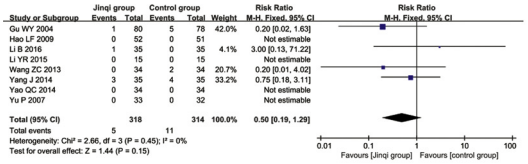
F.2 Sensitivity analysis of TC



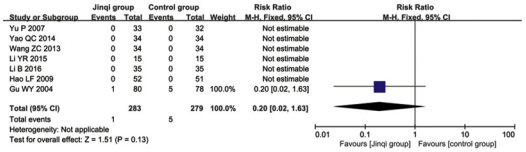
G.1 Forest map of TG

Delete study	MD	95% CI	I^2	P(effect)
Gu WY 2004	-0.29	[-0.42, -0.16]	39%	<0.00001
Hao LF 2009	-0.32	[-0.47, -0.18]	62%	<0.00001
Li T 2012	-0.33	[-0.49, -0.18]	62%	<0.0001
Liu Y 2017	-0.40	[-0.51, -0.30]	0%	<0.00001
Wang ZC 2013	-0.35	[-0.49, -0.20]	65%	<0.00001
Xu J 2008	-0.32	[-0.46, -0.18]	60%	<0.00001
Yao QC 2014	-0.34	[-0.50, -0.19]	64%	<0.0001
Yu P 2007	-0.34	[-0.50, -0.19]	64%	<0.0001

G.2 Sensitivity analysis of TG



H Forest map of total incidence of adverse events



I Forest map of incidence of hypoglycemia

Fig. 3. Secondary outcomes comparison between JQJTT plus conventional therapy group and conventional therapy group.

4.5. LDL-C

The meta-analysis result in LDL-C level is shown in Fig. 3E.1. Five trials[13,18–20,23] enrolling 539 subjects used LDL-C as an outcome. The heterogeneity across trials was significant (I^2 = 93%), so a random-effects model was used for statistical analysis. A meta-analysis showed there was a statistical difference in LDL-C level in favor of JQJTT plus conventional therapy group (n = 539, MD −0.37; 95%CI [−0.63, −0.11]; p = 0.006).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 3E.2). By excluding the original studies item by item from the meta-analysis, and the heterogeneity across studies was still significant. After the removal of the study of Li T 2012,[18] the result of the meta-analysis changed (MD −0.38; 95%CI [−0.80, 0.04]; p = 0.07),which indicated that the results were not stable in LDL-C level.

4.6. TC

The meta-analysis result in TC level is shown in Fig. 3F.1. Eight trials[13,16–20,23,27] enrolling 775 subjects used TC as an outcome. The heterogeneity across trials was significant (I^2 = 86%), so a random-effects model was used for statistical analysis. A meta-analysis showed there was a statistical difference in TC level in favor of JQJTT plus conventional therapy group (n = 775, MD −0.46; 95%CI [−0.85, −0.08]; p = 0.02).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 3F.2). By excluding the original studies item by item from the meta-analysis, and the heterogeneity across studies decreased after the removal of the study of Li T 2012[18] (I^2 = 10%). Therefore, the study of Li T 2012[18] might cause the heterogeneity of this outcome measure (i.e., TC). However, after excluding this study, there was no change in the conclusion of the meta-analysis (MD −0.24; 95%CI [−0.40, −0.08]; p = 0.003). In addition, the result of the meta-analysis changed (MD −0.40; 95%CI [−0.80, 0.00]; p = 0.05) after the removal of the study of Yao QC 2014.[17]

4.7. TG

The meta-analysis result in TG level is shown in Fig. 3G.1. Eight trials[13,16–20,23,27] enrolling 775 subjects used TG as an outcome. The heterogeneity across trials was significant (I^2 = 59%), so a random-effects model was used for statistical analysis. A meta-analysis indicated a statistical difference in TG level in favor of JQJTT plus conventional therapy group (n = 775, MD −0.34; 95%CI [−0.47, −0.20]; p < 0.00001).

In order to analyze stability of the combined result, subsequent sensitivity analysis was performed (Fig. 3G.2). By excluding the original studies item by item from the meta-analysis, and the heterogeneity across studies decreased after the removal of the study of Gu WY 2004,[19] Liu Y 2017[22] (I^2 = 39%, 0%). Therefore, the study of Gu WY 2004,[19] Liu Y 2017[22] might cause the heterogeneity of this outcome measure (i.e., TG). However, after excluding these two studies, there was no change in the conclusion of the meta-analysis (MD −0.29; 95%CI [−0.42, −0.16]; p < 0.00001),[19] (MD −0.40; 95%CI [−0.51, −0.30]]; p < 0.00001),[22] which indicated that the results were stable.

4.8. Adverse events

Eight trials[11,14,16–18,20,25,27] recorded adverse events, four of which reported no adverse events. And one trial reported adverse events, but did not describe the type of adverse events in detail. We used the total incidence of adverse events, incidence of hypoglycemia, liver function impairment and renal function impairment to evaluate the safety of JQJTT. The meta-analysis result in total incidence of adverse events is shown in Fig. 3H. The heterogeneity across trials was non-significant (I^2 = 0%), so a fixed-effects model was used for statistical analysis. According to the result, there was no significant difference between two groups in total incidence of adverse events (n = 632, RR 0.50; 95% CI [0.19, 1.29]). The meta-analysis result in incidence of hypoglycemia is shown in Fig. 3I. The heterogeneity across trials was not applicable, a fixed-effects model was used for statistical analysis. The result showed that there was no significant difference between two groups in incidence of hypoglycemia (n = 562, RR 0.20; 95% CI [0.02, 1.63]). In terms of liver function impairment and renal function impairment, seven trials indicated that no liver and renal impairment events occurred. Li B 2016[10] showed one case appeared mild diarrhea symptom in JQJTT plus conventional therapy group which was relieved without treatment. Gu WY 2004[19] showed one patient in the treatment group and five in the control group developed mild hypoglycemia. And Wang ZC 2013[26] showed two patients in the conventional therapy group had mild edema symptom.

4.9. Subgroup analysis

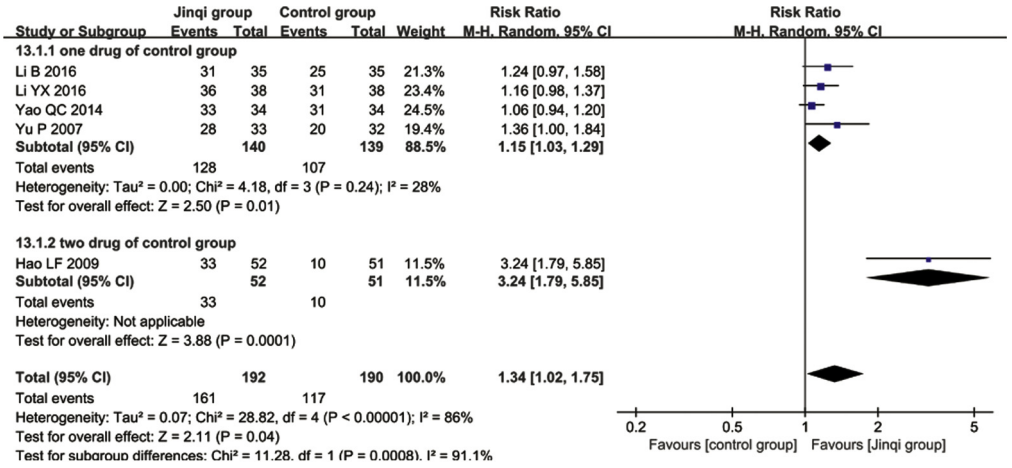
Five studies[11,16–18,26] reported effective rate as an outcome. Subgroup analysis with the treatment duration, the sample size of each comparison group, the kind of conventional therapy was performed to assess the overall risk ratio of effective rate among the five trials. The subgroup analysis with different kinds of conventional therapy (one drug treatment or two drug treatments) showed a statistically significant difference between two comparison groups in both one drug treatment subgroup (n = 279) and two drug treatments subgroup (n = 103) (Fig. 4A). The test for subgroup differences was statistically significant (I^2 91.1%), suggesting this grouping factor may be one of the sources of heterogeneity in meta-analysis. Since all trials were 1:1 two-arm studies, subgroup analysis can be carried out based on the sample size of each comparison group. Four[11,17,18,26] of the five studies[11,16–18,26] had a sample size of each comparison group less than 50, and the sample size was relatively close, with 95% CIs of RR almost overlapping. A study[16] with a sample size of each comparison group more than 50 had less overlap with the remaining four studies in 95% CIs of RR. Therefore, we considered taking the sample size of each comparison group = 50 as a cutoff value for subgroup analysis. The subgroup analysis with the sample size of each comparison group (below or above 50) was performed, and there was a statistically significant difference between two comparison groups in both larger sample size subgroup (n = 103) and smaller sample size subgroup (n = 279) (Fig. 4B). The test for subgroup differences was significant (I^2 91.1%), suggesting that this grouping factor may be one of the sources of heterogeneity in meta-analysis. After consulting experienced clinicians, it was found that 1 month was a node of JQJTT efficacy, so we used 1 month as the cutoff value of treatment duration for subgroup analysis. Subgroup analysis with treatment duration was conducted to assess the overall risk ratio of effective rate. The result showed no statistically significant difference between two comparison groups either in the short-course treatment subgroup (n = 249) or in the long-course treatment subgroup (n = 133) (Fig. 4C). The I^2 value of the test for subgroup differences was 0%, indicating this grouping factor was not the source of heterogeneity in meta-analysis.

4.10. Publication bias

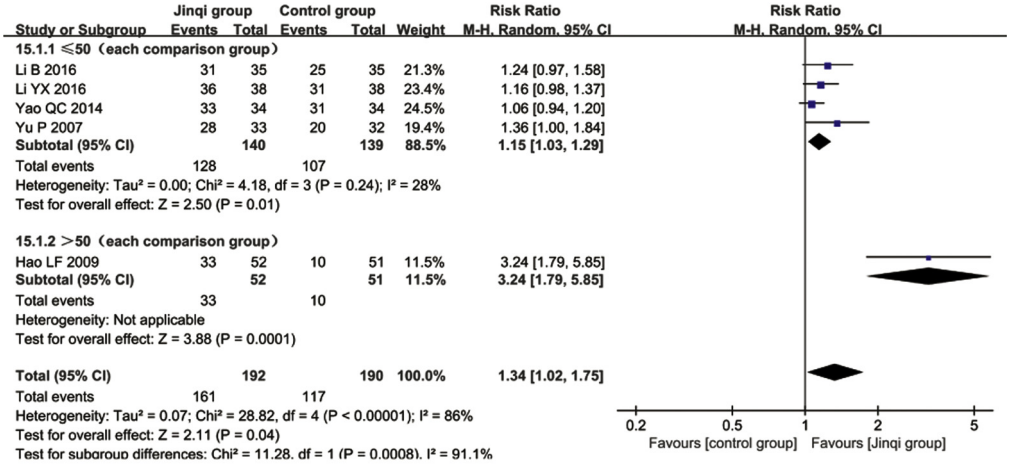
Publication bias was assessed using a funnel plot. And the funnel plot analysis was carried out for the primary outcomes FBG, 2h PG, HbA1c (Fig. 2B.3, C.3, D.3). The analysis results showed moderate asymmetries across studies, which indicated that there may be a potential publication bias.

4.11. Summary of evidence and explanation of result

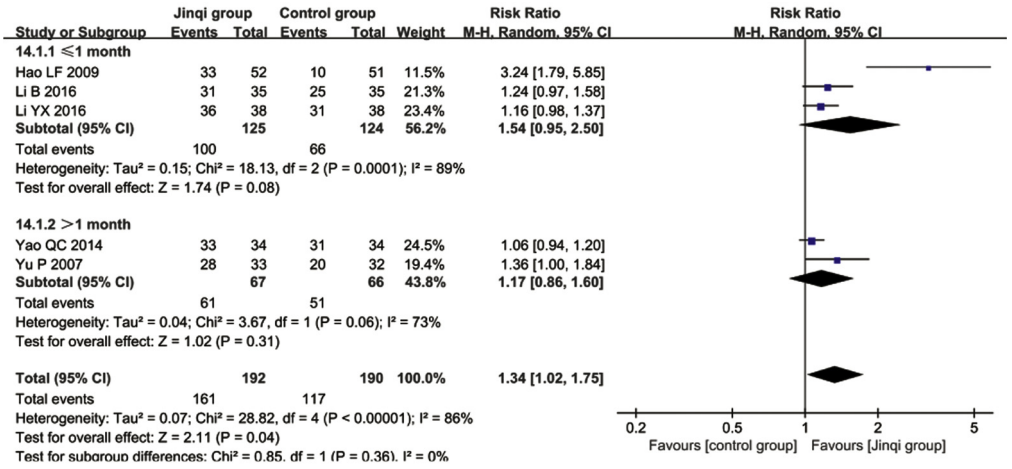
Seventeen RCTs conducted in China with 1425 participants were



A subgroup analysis with the kind of conventional therapy



B subgroup analysis with the sample size of each comparison group



C Subgroup analysis with treatment duration

Fig. 4. Subgroup analysis of effective rate.

included in the meta-analysis to assess the performance of JQJTT plus conventional therapy versus conventional therapy alone in the treatment of T2DM. The results showed that JQJTT combined with conventional therapy had a statistically significant effect on regulating glucose metabolism and lipid metabolism compared to controls (Figs. 3 and 4).

The meta-analysis showed that JQJTT combined with conventional therapy performed better in terms of effective rate. There was a statistically significant reduction associated with FBG, 2h PBG and HbA1c in JQJTT plus conventional therapy group compared to conventional therapy group alone. In terms of FINS, PINS and HOMA-IR, there was a better performance in JQJTT plus conventional therapy group compared to controls. In terms of lipid metabolism, there was a statistically significant improvement associated with LDL-C, TC, TG in JQJTT plus conventional therapy group vs conventional therapy group alone, but no statistical difference in HDL-C level with JQJTT plus conventional therapy versus conventional therapy. No serious adverse events occurred in the included studies, and there was no statistically significant difference in the incidence of adverse events between the JQJTT plus conventional therapy group and conventional therapy group. Sensitivity analysis was conducted for the primary outcomes, and the results showed little change and much overlap in the 95% CIs, suggesting that the results of the meta-analysis were relatively stable. Subgroup analysis indicated that the sample size and the kind of conventional therapy may be the sources of heterogeneity across studies.

With the increasing incidence of T2DM, it has become a worldwide health and economic problem. The development of effective therapies for T2DM is particularly important. In recent years, integrative medicine, including conventional therapy and complementary and alternative therapy, has become more popular in the treatment of T2DM.[28] As an important component of complementary and alternative therapies for T2DM, traditional Chinese medicine has been used in clinical practice for many years.[29] TCPM stands out from TCM because of its refined dosage forms and relatively standardized composition. TCPM contains a variety of active ingredients, so it can play multiple therapeutic effects in the treatment of diabetes through multiple targets and multiple channels.[30] Pang et al.[8] conducted a system review including JQJTT to assess the efficacy and safety of TCPM in treating prediabetes, and the results showed that the combination of TCPM and lifestyle modification had a statistically significant effect on reducing the incidence of diabetes and improving the normalization of blood glucose. And this review also showed that the combination of TCPM and lifestyle modification had a statistically significant reduction in FBG and 2h PG. Gu YM et al.[31] assessed the efficacy and safety of Tianmai Xiaoke Tablet combined with conventional therapy for treating newly diagnosed T2DM, and the results showed that the combination of Tianmai Xiaoke Tablet and conventional therapy had a statistically significant effect on the reduction of FBG, 2h PG, HbA1c and BMI than the conventional therapy alone. The results of our systematic review were similar to the above results, and the combination of JQJTT and conventional therapy had better effects on blood glucose control and lipid metabolism regulation than the conventional therapy alone.

Some studies were performed to elucidate the mechanism of JQJTT in the treatment of T2DM. Chang et al.[32] demonstrated that the mechanism of action of JQJTT for T2DM may be related to inhibiting α-amylase, lipase, α-glucosidase and aldose reductase and scavenging free radicals. Gao et al.[33] found that refined-JQJTT could regulate glycolipid metabolism to reduce insulin resistance and activate AMPK signaling pathway, to improve insulin sensitivity and B cell function. Qian et al.[34] found that Jingqi formula can activate AMPK through a multi-target manner to inhibit TG accumulation to a certain extent.

4.12. Limitations

This systematic review and meta-analysis had certain limitations. First of all, there lacked both the diagnosis of TCM syndromes and the evaluation of TCM symptom improvement in the outcome. Secondly, most of the included studies were small sample size without high methodological quality. Thirdly, the longest intervention duration in the included studies was six months, which was not enough to assess the microvascular and macrovascular complications associated with T2DM. Fourthly, most of the included studies did not clearly describe dropouts and withdrawals. Fifthly, the protocol of included studies were not registered or published. Sixthly, no post-treatment follow-up was performed in all included studies. Seventh, the heterogeneity across the studies was significant in the meta-analysis, which may influence the evaluation of therapeutic effect. Eighth, all the included studies were conducted in China, so we cannot evaluate the efficacy of JQJTT in treating diabetes in other ethnic groups. Ninth, some studies did not adequately document adverse events, and the reported safety outcomes were relatively vague. Tenth, the control group did not receive a placebo, and the absence of blinding method may result in biased results. Eleventh, no clear definition of hypoglycemia was given in all the original studies, so we didn't know an adverse event of hypoglycemia in the original studies was confirmed by self-reported symptoms or by laboratory blood tests, which may lead to bias in the safety evaluation of JQJJT. In this systematic review, pharmaceutical companies producing JQJTT were not contacted to further determine whether there were any unpublished related studies. Based on the above statement, the results should be interpreted with caution. Therefore, in the future, long-term and multinational clinical trials with larger sample sizes and higher methodological quality are needed to further evaluate the effectiveness and safety of JQJTT combined with conventional therapy for T2DM.

4.13. Implications for practice

The results of this meta-analysis showed JQJTT combined conventional therapy have a better performance for T2DM treatment than the conventional therapy alone. However, due to the limitations of meta-analysis, it's too early to make it a clinical recommendation, and more RCTs with larger sample sizes, higher methodological quality are needed to support this result in the future. In addition, all these included studies were carried out in China, which made the results unable to be generalized to other ethnic groups, suggesting that large-scale RCTs should be conducted across regions and countries in the future to further explore the efficacy and safety of JQJTT in other ethnic groups. As one of the TCPMs in the treatment of T2DM, JQJTT belongs to the category of traditional Chinese medicine compound prescription and has the function of clearing heat and promoting qi (vital energy). Traditional Chinese medicine compound prescription is composed of a variety of Chinese herbal medicines. In the theory of TCM, the function of traditional Chinese medicine compound prescription is determined by the action of each drug and the interaction between them. JQJTT has the function of clearing heat and fortifying qi, which is determined by the effect of three drugs, namely Radix Astragali (Huang Qi), Rhizoma Coptidis (Huang Lian), lonicera japonica (Jin Yin Hua), and their compatibility with each other. The function of clearing heat and fortifying qi of JQJTT has been widely recognized in China. In addition, clearing heat and fortifying qi belong to the concept of TCM theory, which is different from the action mechanism of chemical drugs. In future studies, researchers should not only pay attention to the effect of JQJTT on glucose and lipid metabolism, but also pay attention to the improvement of TCM syndromes.

5. Conclusion

The available evidence indicates that JQJTT combined with conventional therapy for T2DM has a good performance in regulating glycolipid metabolism and improving insulin resistance. However, due to the limitations of the current system review, it is necessary to perform more RCTs with higher methodological quality, larger scale and

cross-nation in the future to further prove the effectiveness and safety of JQJTT.

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