Clinical Efficacy and Safety of Yi-Shen-Hua-Shi Granule for Diabetic Kidney Disease: A Cohort Study

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Research

Keywords: Yi-Shen-Hua-Shi granule, Irbesartan, Diabetic Kidney Disease

Posted Date: December 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-113813/v1>

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Abstract

Background: The present study aims to explore the relative efficacy and safety of Yi-Shen-Hua-Shi (YSHS) granule in diabetic kidney disease (DKD) patients.

Methods: A total of 260 DKD patients with the urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g and estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73 m² were included. 130 patients receiving YSHS plus irbesartan and 130 patients with irbesartan alone. The primary outcomes were included serum creatinine (Scr), 24-hour urinary protein (24h UTP), UACR, and the overall response rate (ORR). The secondary outcomes included fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL-C).

Results: At the end of 12 weeks, compared with the controls, the YSHS group could effectively improve the level of 24h UTP ($P = 0.007$), UACR ($P = 0.001$), FBG ($P = 0.024$), HbA1c ($P = 0.005$), TC ($P = 0.018$), TG ($P = 0.001$), and LDL-C ($P = 0.034$). The ORR in the YSHS group and control group was 47 % versus 30 % at 12 weeks ($P = 0.005$), respectively. There was no statistical difference in major adverse reactions between the two groups during treatment.

Conclusions: The YSHS granule has significant curative effects on DKD, especially in reducing proteinuria, improving blood glucose and lipid metabolism, with no obvious adverse reactions.

1. Introduction

Diabetic kidney disease (DKD) are the leading cause of end-stage kidney disease (ESKD) in most developed countries and developed in 20–30% of patients with diabetes [1]. Many patients with DKD have residual albuminuria, and the ESKD risk showed a clear dependence on albuminuria reduction [2, 3]. Specific treatment of patients with DKD can be divided into 4 major arenas: cardiovascular risk reduction, glycemic control, blood pressure control, and inhibition of the renin-angiotensin system (RAS) [4]. Although these medications are effective, many patients still have residual albuminuria and are at increased risk of disease progression [5]. Even with albuminuria-lowering medication such as losartan, about 40% patients had a dissociation of antihypertensive and anti-albuminuric responses [6]. Therefore, new drugs for albuminuria are needed to address unmet needs in the management of DKD.

Yi-Shen-Hua-Shi (YSHS) granule is a modern Chinese patent drug for treating chronic glomerulonephritis (CGN), developing by Guangzhou Consun pharmaceutical Co. Ltd [7]. It is derived from a traditional Chinese medicine (TCM) formula Sheng-Yang-Yi-Wei decoction that is used in the dosage form of decoction and is composed of 16 herbs, includes *ginseng*, *astragalus*, *atractylodes*, *poria*, *alisma*, *duhuo*, and other components. It has the effects of boosting spleen, nourishing kidney, dampening, diuretic and swelling. YSHS also helps and oxidative stress in patients with DKD. Previous clinical studies have shown that YSHS can effectively reduce reducing proteinuria and hematuria, improve microcirculation, stabilize renal function, and have fewer adverse reactions in the treatment of IgA and CGN [8, 9].

Although YSHS has been treating kidney disease for more than twenty years, there is still a lack of clinical research on large samples of DKD [7, 10, 11]. Therefore, we provided a new cohort study to evaluate the clinical efficacy and safety of YSHS granule + irbesartan versus irbesartan in patients with DKD.

2. Methods

2.1. Ethics committee statement

This trial was approved by the Regional Ethics Committee of the Second Affiliated hospital of Nanchang University with the approval number: No. [2019] 044. Due to the retrospective nature of the study, informed consent was abandoned. The design of the study fully considered the principles of security and fairness. There was no competing interest in this research.

2.2. Patients

This study was a retrospective cohort study with two hundred sixty patients. We collected all DKD patients between June 2012 and June 2019 in the Department of Nephrology, the Second Affiliated Hospital of Nanchang University, Jiangxi Province, China. The inclusion criteria were as follows: (1) patients (aged 30–85 years) had type 2 diabetes by the diagnostic standard of American Diabetes Association and DKD by the staging criteria of Mogensen [12, 13], (2) patients in the YSHS group had spleen-kidney yang deficiency (Pi shen yang xu in Chinese) [14], (3) a urinary albumin-to-creatinine ratio (UACR) in first morning void of 30–3000 mg/g, (4) estimated glomerular filtration rate (eGFR) > 30 ml/min per 1.73 m², (5) hemoglobin A1c (HbA1c) less than 11.0% (97 mmol/mol), and (6) a follow-up time was up to 12 weeks. The exclusion criteria were: (1) known renal disease due to conditions other than diabetes, autoimmune disorder or requirement for immunosuppressive therapy malignancy, (2) significant obstructive uropathy, other renal impairment not related to parenchymal renal disorder or disease of the kidney, (3) Serious cardiovascular and cerebrovascular diseases, Severe hemorrhage and coagulopathy, (4) pregnancy or lactation.

2.3. Treatment protocol

In the control group (n = 130), all patients received routine treatment, such as hypoglycemic, ester-regulating, antihypertensive drugs other than angiotensin receptor blockers (ARBs), and irbesartan 75 to 150 mg orally twice daily. On the basis of the treatment of the control group, the YSHS group (n = 130) were accepted YSHS granules (Guangzhou Consun pharmaceutical, China) 10 g, oral, 3 times/day. The duration of treatment in both groups was 12 weeks.

2.4. Follow-up and outcomes

Follow-up visits were scheduled at weeks 6 and 12 after the initiation therapy described above. We predefined the potential baseline indexes, including sex, age, serum albumin level, 24-hour urinary total protein (24 h UTP), UACR, serum creatinine (Scr) level, eGFR, fasting blood glucose (FBG), HbA1c, blood pressure (BP), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C). The primary

efficacy endpoints were Scr level, UACR, 24 h UTP, and the overall response rate [ORR, the 24 h UTP quantitative decline was $\geq 50\%$ or UACR returned to normal ($< 30 \text{ mg/ g}$)]. The secondary outcomes included FBG, HbA1c, TC, TG, LDL-C.

2.5. Statistical analysis

Categorical variables were summarized using proportions and compared using a Pearson chi-square test. Normally distributed variables are expressed as mean $\pm$ standard deviation (SD) and compared using independent or paired t-tests where appropriate. Nonparametric continuous variables are expressed as the median of the interquartile range (IQR, 25th and 75th percentiles) and compared using nonparametric tests when needed. The Kaplan-Meier curves were used to describe Time-to event data, and log-rank tests were used to compare differences between groups. Graph Pad Prism (version 7.0) and SPSS (version 23.0) were used for statistical analysis. Statistical significance was indicated by two-sided *P* values < 0.05 .

3. Results

3.1. Study Participants

We identified two hundred sixty participants (130 patients receiving YSHS granule plus irbesartan and 130 patients with irbesartan) that satisfied the criteria (Fig. 1). During the follow-up period, seven censored patients who received YSHS + irbesartan were missing important data (24-hour UTP and Scr level), and six patients in the irbesartan group lacked significant data (UAER and medication administration record). The above patients are excluded. No significant difference in baseline data between the two cohorts (Table 1). In the recent months before the start of follow-up, no included patients had undergone a basic angiotensin-converting enzyme inhibitors (ACEI) / ARB treatment or other Chinese patent medicine to protect kidney function. There was no significant difference in other antihypertensive drug use between the 2 groups.

Table 1

Clinical features of participants at baseline. Note: Values for categorical variables were given as count (percentage); values for continuous variables, as mean $\pm$ standard deviation or median [IQR]. Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range.

Characteristic	YSHS group (n = 130)	Control group (n = 130)	P Value
Men	75 (55)	79 (51)	0.614
Duration of diabetes mellitus	8.6 $\pm$ 6.5	7.8 $\pm$ 5.9	0.488
Asian	130	130	1
Age (y)	60 $\pm$ 13	59 $\pm$ 12	0.358
Systolic blood pressure (mmHg)	119.6 $\pm$ 9.4	120.0 $\pm$ 7.7	0.765
Diastolic blood pressure (mmHg)	74.7 $\pm$ 7.2	74.1 $\pm$ 6.9	0.574
Serum creatinine (μ mol/L)	90.9 $\pm$ 31.9	88.7 $\pm$ 28.0	0.579
eGFR (ml/min per 1.73 m ²)	91.7 $\pm$ 28.9	92.8 $\pm$ 25.8	0.814
Serum albumin (g/L)	40.4 $\pm$ 4.1	41.2 $\pm$ 3.6	0.117
Urine protein (g/d)	1.30 (0.65 to 2.56)	1.05 (0.48 to 1.62)	0.735
Urinary albumin-to-creatinine ratio (mg/g)	264.64 (111.15 to 578.65)	236.34 (142.93 to 549.31)	0.802
Fasting glucose (mmol/L)	6.52 (5.71 to 7.64)	6.76 (5.72 to 7.56)	0.628
HbA1c (%)	6.5 (5.8 to 7.5)	6.6 (6.0 to 7.3)	0.387
Total cholesterol (mmol/L)	4.80 (4.41 to 5.29)	4.89 (4.05 to 5.78)	0.702
Triglycerides (mmol/L)	1.98 (1.49 to 2.19)	1.67 (1.12 to 2.25)	0.150
Low-density lipoprotein (mmol/L)	2.67 (2.26 to 3.08)	2.69 (2.28 to 3.16)	0.871
Medications			
Yi-Shen-Hua-Shi granule	130	0	-
Irbesartan	130	130	1
Calcium channel blockers	63 (49)	54 (42)	0.262
β -receptor antagonists	21 (16)	17 (13)	0.483
α -receptor blockers	8 (6)	11 (8)	0.475
Diuretics	7	6	0.754
Metformin	72 (55)	61 (47)	0.172
Thiazolidinediones	45 (35)	57 (44)	0.127

Characteristic	YSHS group (n = 130)	Control group (n = 130)	<i>P</i> Value
DPP-4 inhibitors	1 (1)	0 (0)	0.316
Fast-acting insulin	43	38	0.503
Long-acting insulins or insulin combinations	31	28	0.657
HMG-CoA reductase inhibitors	52 (40)	49 (38)	0.703
Aspirin	8	6	0.583

3.2. Primary outcome measures

In the YSHS group, the Scr level decreased by a median of 6.91 $\mu\text{mol/L}$ (IQR, -13.60 to 0.63 $\mu\text{mol/L}$) at 6 weeks, and respectively, the control group increased 1.20 $\mu\text{mol/L}$ (IQR, -2.20 to 8.60 $\mu\text{mol/L}$) ($P= 0.004$, Table 2, Fig. 2A). There was no statistical difference between the two groups regarding the concentration of Scr at the end of trial (IQR was - 12.31 to 0.95 $\mu\text{mol/L}$ and - 6.47 to 2.06 $\mu\text{mol/L}$ in the YSHS and control groups, respectively) ($P= 0.179$, Table 2, Fig. 2A). There was no end-stage renal failure (ESRF) in each group.

Table 2

Summary of primary outcomes, secondary outcomes, and adverse events. Abbreviations: UACR, urinary albumin-to-creatinine ratio; ORR, overall response rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein.

End Point	YSHS group (n = 130) End Point Value	Control group(n = 130) End Point Value	P Value
<i>Primary outcomes</i>			
Change in Serum creatinine at week 6 (μmol/L)	-6.91 (-13.60 to 0.63)	1.20 (-2.20 to 8.60)	0.004
Change in Serum creatinine at week 12 (μmol/L)	-3.38 (-12.31 to 0.95)	-1.89 (-6.47 to 2.06)	0.179
Change in proteinuria at week 6 (g/d)	-0.35 (-0.70 to -0.15)	-0.04 (-0.20 to 0.33)	0.176
Change in proteinuria at week 12 (g/d)	-0.50 (-1.05 to -0.30)	-0.08 (-0.19 to -0.02)	0.007
Change in UACR at week 6 (mg/g)	-63.45 (-183.17 to -20.09)	-54.81 (-114.09 to 6.35)	0.374
Change in UACR at week 12 (mg/g)	-113.48 (-237.62 to -40.43)	-28.66 (-89.48 to 6.96)	0.001
ORR at week 6 (%)	20 (15)	18 (14)	0.726
ORR at week 12 (%)	61 (47)	39 (30)	0.005
<i>Secondary outcomes</i>			
Change in FBG at week 12 (mmol/L)	-0.57 (-1.44 to -0.18)	-0.39 (-0.90 to 0.11)	0.024
Change in HbA1c at week 12 (%)	-0.50 (-1.08 to -0.20)	-0.20 (-0.70 to 0.10)	0.005
Change in TC at week 12 (mmol/L)	-0.55 (-1.11 to -0.10)	-0.26 (-1.11 to 0.48)	0.018
Change in TG at week 12 (mmol/L)	-0.52 (-0.78 to -0.07)	-0.07 (-0.51 to 0.20)	0.001
Change in LDL-C at week 12 (mmol/L)	-0.44 (-0.77 to -0.16)	-0.21 (-0.64 to 0.13)	0.034
<i>Adverse events</i>			
Nausea or vomiting	2 (2)	3 (2)	0.652
Insomnia	1 (1)	3 (2)	0.314
Abnormal liver function	0 (0)	2 (2)	0.156
Rash	2 (2)	1 (1)	0.561
Data Availability Statement			

Proteinuria decreased by a median of 0.35 g/d (IQR, -0.70 to -0.15 g/d) and 0.04 g/d (IQR, -0.20 to 0.33 g/d) at 6 weeks in the YSHS and control groups, respectively ($P = 0.176$, Table 2). At the 12th week of follow-up, proteinuria decreased by a median of 0.50 g/d (IQR, -1.05 to -0.30 g/d) and 0.08 g/d (IQR, -0.19 to -0.02 g/d) in the YSHS and control groups, respectively ($P = 0.007$, Table 2).

At the 6-week follow-up, there was no significant difference in UACR between groups (IQR was -183.17 to -20.09 g/g and -114.09 to 6.35 g/g in the YSHS and control groups, respectively) ($P = 0.374$, Table 2). At the end of 12 weeks, the YSHS group remarkably reduced UACR when compared with control group. UACR decreased by a median of 113.48 g/g (IQR, -237.62 to -40.43 g/g) and 28.66 g/g (IQR, -89.48 to 6.96 g/g) in the YSHS and control groups, respectively ($P = 0.001$, Table 2).

The ORR in the YSHS group and control group was 15% versus 14% at 6 weeks ($P = 0.726$) and 47% versus 30% at 12 weeks ($P = 0.005$), respectively. And the Kaplan-Meier analysis for the probability of overall response was statistically significant between the two groups at week 12 ($P = 0.006$, Fig. 3).

3.3. Secondary outcome measures

At the end of 12 weeks, the YSHS group was more conducive to lower the FBG, HbA1c, TC, TG, and LDL-C than the control group (Table 2, Fig. 2). The FBG decreased by a median of 0.57 mmol/L (IQR, -1.44 to -0.18 mmol/L) and 0.39 mmol/L (IQR, -0.90 to 0.11 mmol/L) in the YSHS and control groups, respectively ($P = 0.024$). Compared with the control group (IQR, -0.70 to 0.10%), the YSHS group could remarkably reduce HbA1c (IQR, -1.08 to -0.20%) ($P = 0.005$). The TC decreased by a median of 0.55 (IQR, -1.11 to -0.10 mmol/L) and 0.26 mmol/L (IQR, -1.11 to 0.48 mmol/L) in the YSHS and control groups, respectively ($P = 0.018$). The TG decreased by a median of 0.52 (IQR, -0.78 to -0.07 mmol/L) and 0.07 mmol/L (IQR, -0.51 to 0.2 mmol/L) in the YSHS and control groups, respectively ($P = 0.001$). The LDL-C decreased by a median of 0.44 (IQR, -0.77 to -0.16 mmol/L) and 0.21 mmol/L (IQR, -0.64 to 0.13 mmol/L) in the YSHS and control groups, respectively ($P = 0.034$).

3.4. Adverse reaction

All adverse events occurring between study inclusion and last follow-up visit were observed (Table 2). During the 12-weeks treatment, the main adverse reactions of the two groups of patients included nausea, vomiting, insomnia, abnormal liver function, and rash. The differences were not statistically significant. 2% of patients in the YSHS group had nausea or vomiting, compared with 2% in the control group ($P = 0.652$). Between the two groups, the insomnia rates in the YSHS and control groups were 1% and 3% ($P = 0.314$), and the rash was 2% and 1% ($P = 0.561$). The proportion of patients with abnormal liver function in the YSHS group and control group was 0% versus 2%, respectively ($P = 0.156$).

4. Discussion

DM has long been known to be an important cause of CKD [15]. The pathophysiology that leads to the development of diabetic nephropathy and eventually ESKD follows from the DM, leading to the generation and circulation of advanced glycation end products, processing of growth factors, and

hemodynamic and hormonal changes [4]. These changes result in glomerular hyperfiltration, glomerular hypertension, renal hypertrophy, and altered glomerular composition, with clinical manifestations of albuminuria and hypertension (Fig. 4). Drugs that block the RAS, such as ACEI and ARBs, are recommended as first-line antihypertensive therapy for patients with diabetic kidney disease and overt albuminuria [16]. However, it is not enough to alleviate proteinuria by ACEI / ARB. A few researches showed that TCM combined with ACEI / ARB seems to have better efficacy compared with ACEI / ARB alone, especially in reducing urine protein and delaying renal function [10, 17–19].

TCM advocates dialectical treatment, focusing on the overall concept. It believes that protein is a subtle substance of the human body, which is metabolized by the spleen, stored by the kidney, and the formation of proteinuria is related to the deficiency of the spleen and kidney [7]. YSHS granule is derived from a TCM formula Sheng-Yang-Yi-Wei decoction with 16 herbs, which first documented in a TCM classic *Nei-Wai-Shang-Bian-Huo-Lun* issued in 1247. The formula is able to tonify yang and spleen ('Sheng Yang Bu Pi' in Chinese), replenish renal and resolve dampness ('Yi Shen Hua Shi' in Chinese), and increase urine excretion to relieve edema ('Li Shui Xiao Zhong' in Chinese). In addition, Zhao Jie et al. [7] indicated that YSHS granule showed a therapeutic effect in a rat model of CGN, and inhibition of the TGF β / Smad signaling pathway was elated in the mechanism of action of the granule (Fig. 4). And the result demonstrated that YSHS granule treatment ameliorated pathological damages, such as glomerular capsule exfoliative cell aggregation, vacuolar deformation of renal tubular epithelial cell, protein cases of kidney tubules, and podocyte injury.

We first conducted a cohort study with two hundred sixty patients to evaluate the effectiveness and safety of Yi-Shen-Hua-Shi (YSHS) granule combined with irbesartan in the treatment of DKD. Our results indicated that compared with the controls, the YSHS granule combined with irbesartan group could obviously improve the ORR and reduce 24 h UTP and UACR at the end of the follow-up. Another work base on animal experiments found that YSHS could up-regulate the expression of Nephtrin and Podocin in podocytes and decrease the expression of PDGFRI3 in the kidney, reverse the damage of the podocyte diaphragm, reduce urine protein excretion, increase creatinine clearance, and have an adjunctive therapy for the renal protective effect [20].

As for secondary outcome measures, the present study suggested that the YSHS group is superior to the control group in improving blood glucose and lipid metabolism. And the above results have been supported by previous domestic clinical studies [10–11]. In summary, YSHS also plays a role in the treatment of diabetes, hyperlipidemia, and other complications.

There were several limitations to this study. Firstly, the course of therapy and follow-up were quite short, thus the long-term effect of YSHS remains to be negotiated. Secondly, missing data were inevitable. However, they would tend to bias the results toward the null hypothesis.

5. Conclusion

YSHS granule combined with irbesartan in the treatment of DKD can effectively reduce the level of albuminuria, protect the renal function, improve the blood glucose and lipid metabolism, which is worthy of application and promotion in clinical practice.

Abbreviations

YSHS

Yi-Shen-Hua-Shi

DKD

Diabetic kidney disease

UACR

Urinary albumin-to-creatinine ratio

eGFR

Estimated glomerular filtration rate

Scr

Serum creatinine

24 h UTP

24-hour urinary protein

ORR

The overall response rate (ORR)

FBG

Fasting blood glucose

HbA1c

Hemoglobin A1c

TC

Total cholesterol

TG

Triglyceride

LDL-C

Low-density lipoprotein

ESKD

End-stage kidney disease

RAS

Renin-angiotensin system

CGN

Chronic glomerulonephritis

TCM

Traditional Chinese medicine

ARBs

Angiotensin receptor blockers

BP
Blood pressure
SD
Standard deviation
IQR
Interquartile range
ACEI
Angiotensin-converting enzyme inhibitors
ESRF
End-stage renal failure

Declarations

6. Ethics declarations

This trial was approved by the Regional Ethics Committee of the Second Affiliated hospital of Nanchang University with the approval number: No. [2019] 044. Due to the retrospective nature of the study, informed consent was abandoned.

6.1 Ethics approval and consent to participate

Not applicable.

6.2 Consent for publication

Not applicable.

7. Availability of data and materials

The datasets used in the present study are available from the corresponding author on reasonable request.

8. Competing interests

The authors declare that they have no competing interests.

9. Funding

This work was supported by the National Natural Science Foundation of China (No. 81970583), the Nature Science Foundation of Jiangxi Province (No. 20181BAB205016), the Traditional Chinese Medicine Technology Project of Jiangxi Province (No. 2019A127), and the Projects in the Second Affiliated Hospital of Nanchang University (No. 2019YNLZ12008).

10. Authors' Contributions

LYB performed the data collection, reviewed articles, and wrote the manuscript. YZP and WK completed the data analysis, reviewed articles and provided the second views during the manuscript preparation. HTL and LX performed the data collection. XGS designed the study and revised the manuscript. All authors have read and approved this information before submission.

11. Acknowledgements

Not applicable.

12 Author information

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Figures

Figure 1

Flow diagram for inclusion of participants. Individuals who did not meet inclusion criteria were excluded. Of the remaining 260 patients, 130 with Yi-Shen-Hua-Shi granule plus irbesartan could be matched to 130

with irbesartan only.

Figure 1

Flow diagram for inclusion of participants. Individuals who did not meet inclusion criteria were excluded. Of the remaining 260 patients, 130 with Yi-Shen-Hua-Shi granule plus irbesartan could be matched to 130 with irbesartan only.

Figure 2

Comparison of the decrease levels of Scr, FBG, HbA1c, TC, TG, and LDL-C before and after treatment in the two groups. (A) The decrease levels of Scr prior and post treatment in 2 groups. (B) The decrease levels of FBG prior and post treatment in 2 groups. (C) The decrease levels of HbA1c prior and post treatment in 2 groups. (D) The decrease levels of TC prior and post treatment in 2 groups. (E) The decrease levels of TG prior and post treatment in 2 groups. (F) The decrease levels of LDL-C prior and

post treatment in 2 groups. Compared with the control group, # $P < 0.05$. Compared with the same group prior treatment, * $P < 0.05$, ** $P < 0.01$. Scr, serum creatinine; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein.

Figure 2

Comparison of the decrease levels of Scr, FBG, HbA1c, TC, TG, and LDL-C before and after treatment in the two groups. (A) The decrease levels of Scr prior and post treatment in 2 groups. (B) The decrease

levels of FBG prior and post treatment in 2 groups. (C) The decrease levels of HbA1c prior and post treatment in 2 groups. (D) The decrease levels of TC prior and post treatment in 2 groups. (E) The decrease levels of TG prior and post treatment in 2 groups. (F) The decrease levels of LDL-C prior and post treatment in 2 groups. Compared with the control group, # $P < 0.05$. Compared with the same group prior treatment, * $P < 0.05$, ** $P < 0.01$. Scr, serum creatinine; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein.

Figure 3

Kaplan-Meier analysis for the probability of overall response in patients with diabetic kidney disease treated with Yi-Shen-Hua-Shi (YSHS) granule plus irbesartan versus irbesartan.

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Kaplan-Meier analysis for the probability of overall response in patients with diabetic kidney disease treated with Yi-Shen-Hua-Shi (YSHS) granule plus irbesartan versus irbesartan.

Figure 4

Yi-Shen-Hua-Shi (YSHS) on the pathophysiology of diabetic kidney disease (DKD). The pathophysiology leading to the development of DKD follows from the diabetic milieu leading to the generation and circulation of advanced glycation end products, elaboration of growth factors, and hemodynamic and hormonal changes. YSHS down-regulated proteins levels of TGFβ1, phospho-Smad2/3 (Thr 8) and Smad4, and ameliorated pathological damages, such as glomerular capsule exfoliative cell aggregation, vacuolar deformation of renal tubular epithelial cell, protein cases of kidney tubules, and podocyte injury. The pathophysiology of DKD reproduced from Kausik et al [Diabetic nephropathy. Am J Kidney Dis. 2018;71(6):884-895]. Pathological pictures reproduced from Najafian et al [Diabetic nephropathy. Am J Kidney Dis. 2015;66(5):e37-e38].

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