Increased levels of YKL-40 in patients with diabetes mellitus: a systematic review and meta-analysis

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Keywords: diabetes mellitus, YKL-40, diabetic nephropathy, meta-analysis

DOI: https://doi.org/10.21203/rs.3.rs-66065/v2

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Abstract

Background: Diabetes mellitus (DM) could be classified as type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) and others according to etiology and pathology. Diabetic nephropathy (DN) is one of the most serious complications of DM. YKL-40 is a marker of inflammation and some studies have indicated that DM was related with inflammation. The objective of our study is to perform a systematic review and meta-analysis to confirm the relationship between YKL-40 and DM as well as DN.

Methods: Pubmed, Embase, CNKI and Chinese wanfang databases were searched for eligible studies by two independent authors. Studies were included in this meta-analysis if they fulfilled the following inclusion criteria: (1) a study involving the role of YKL-40 in DM (or DN) designed as a case-control study or cohort study; (2) the data of serum YKL-40 levels were available; (3) studies were published in English or Chinese.

Results: Twenty-five studies involving 2498 DM patients and 1424 healthy controls were included. Compared with healthy controls, DM patients had significantly higher levels of YKL-40 (DM: SMD=1.62, 95%CI, 1.08 to 2.25, P=0.000; GDM: SMD=2.85, 95%CI, 1.01 to 4.70, P=0.002). Additionally, DM patients with different degree of albuminuria had significantly higher levels of YKL-40 compared with healthy controls (normoalbuminuria: SMD=1.58, 95%CI, 0.59 to 2.56, P=0.002; microalbuminuria: SMD=2.57, 95%CI, 0.92 to 4.22, P=0.002; macroalbuminuria: SMD=2.69, 95%CI, 1.40 to 3.98, P=0.000) and serum YKL-40 levels increased with increasing severity of albuminuria among DM patients (microalbuminuria vs normoalbuminuria: SMD=1.49, 95%CI, 0.28 to 2.71, P=0.016; macroalbuminuria vs microalbuminuria: SMD=0.93, 95%CI, 0.34 to 1.52, P=0.002).

Conclusions: DM patients have higher levels of YKL-40 compared with healthy controls. Additionally, levels of YKL-40 are significantly higher in DM patients with different degree of albuminuria than in the healthy controls and the levels of YKL-40 are positively related with the severe degree of albuminuria. Therefore, our current meta-analysis suggests that their sera should be detected for YKL-40, if DM, especially DN, is suspected in patients.

Background

Diabetes mellitus (DM) is a common disease in the modern society. According to etiology and pathology, DM could be classified as type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) and others. T1DM is a genetic disease and usually occurs in adolescence. It is characterized by absolute insulin deficiency resulting from the destruction of the β cells of the pancreas. T2DM accounts for 90% to 95% of people with DM. T2MD is often to be found in adults, especially in those who are obese. Insulin resistance and relative insulin deficiency are main cause of T2DM [1, 2]. GDM is defined as glucose intolerance with onset or first recognition during pregnancy [3]. Women with GDM tend to develop T2DM after pregnancy. A meta-analysis conducted by Catherine Kim et al. showed that woman with GDM had a rapid increase in the cumulative incidence of T2DM in the first 5 years after delivery, ranging from 2.6% to 70% [4]. Diabetic nephropathy (DN), defined by low estimated glomerular filtration rate (<60 mL/min/1.73 m² for 3 months or more) or albuminuria (urinary albumin-to-creatinine ratio ≥30 mg/g) in the setting of DM [5], is one of the most serious complications of DM. Previous epidemiological studies have indicated that 25% to 40% of patients with T1DM and 5% to 40% of patients with T2DM ultimately develop DN [6, 7]. The pathology of DM is not totally understood. Some studies have indicated that DM was related with inflammation [8, 9].

YKL-40 is also called human cartilage glycoprotein-39 (HCgp-39), and its crystal structure has been represented [10, 11]. Recently, YKL-40 is a marker of inflammation. In vivo, CD 16+ monocytes are a source of YKL-40 and transcription factor Sp1 plays an important role in regulating of YKL-40 [12, 13]. In addition, YKL-40 is secreted by chondrocytes, synovial cells and neutrophils [14]. In vitro, YKL-40 is secreted by various cells, including vascular smooth muscle cells (VSMCs), activated macrophages and macrophages during late stages of differentiation [15].

We assume that there might be an association between DM and YKL-40 since YKL-40 is a new inflammatory marker. Recently, plenty of studies have explored the relationship of DM and YKL-40. But the conclusions of these studies were inconsistent. The objective of our study is to perform a systematic review and meta-analysis to confirm the relationship between YKL-40 and DM as well as DN.

Materials And Methods

Literature search

Pubmed, Embase, CNKI and Chinese wanfang databases were searched for eligible studies published before April 2020 using combinations of the following terms: diabetes; YKL-40; HC gp-39. All studies were retrieved by two independent reviewers and disagreements were solved by discussion.

Study selection

Studies were included in this meta-analysis if they fulfilled the following inclusion criteria: (1) a study involving the role of YKL-40 in DM (or DN) designed as a case-control study or cohort study; (2) the data of serum YKL-40 levels were available (mean/standard deviation or median/range or median/interquartile interval was provided); (3) studies were published in English or Chinese. In case of duplicated data, only the most recent and complete study was included.

Date extraction and statistical analysis

Some of the included studies provided YKL-40 concentration by median and range (or interquartile interval), which were converted to mean (SD) by estimation methods [16]. The statistical software R was used during the data estimation.

Standardized mean differences (SMD) with 95% confidence interval (CI) was calculated to compare the levels of serum YKL-40 in the DM (or DN) patients with the levels in healthy controls (P<0.05 was considered statistically significant). The between-study heterogeneity was assessed by chi-square statistic and
Discussion

Egger's tests were over 0.05, suggesting that publication bias was not evident in our meta-analysis. Funnel plot and Egger's test were conducted to evaluate the potential publication bias. There was no obvious funnel plot asymmetry and all the P values of the Publication bias not associated with GDM when the study by Xun Shengli et al. [36] was deleted. The results did not change in various subgroups, and the value of $I^2$ remained high in various subgroups, with the exception of one subgroup for studies based on population of Asia.

Association between serum YKL-40 levels and DM

Totally, 12 studies showed an association between the serum YKL-40 levels and DM. The meta-analysis results indicated that the serum YKL-40 levels were significantly higher in DM patients compared with healthy controls (SMD=1.62, 95%CI,1.08 to 2.25, P=0.000) (Figure 2). The Galbraith plot was used because of the notable heterogeneity. But the major source of heterogeneity could not be found since too many of the studies were outliers (Figure 3). Furthermore, subgroup analyses by type of DM, region and age showed that YKL-40 levels were still higher in DM patients than those in healthy controls. The value of $I^2$ remained high in various subgroups, with the exception of one subgroup for studies based on population of Asia.

Association between serum YKL-40 levels and GDM

Owing to significant heterogeneity, we used the random-effects model. The pooled SMD was 2.85 (95%CI, 1.01 to 4.70, P=0.002), which indicated that the serum YKL-40 concentrations were significantly higher in GDM patients compared with healthy pregnancies (Figure 4). The source of heterogeneity was hard to be found by the Galbraith plot because the studies were too dispersive. However, when performing sensitivity analysis by sequential omission of individual studies, YKL-40 was not associated with GDM when the article by Xun Shengli et al. [36] was removed. The pooled SMD was 0.64 (95%CI, -0.28 to 1.56) (P>0.05).

Association between serum YKL-40 levels and albuminuria in DM patients

There were 7,8 and 7 studies analyzing the relationship between serum YKL-40 levels and normoalbuminuria, microalbuminuria and macroalbuminuria, respectively. The forest plot with a random-effects model showed that DM patients with different degree of albuminuria had significantly higher levels of YKL-40 compared with healthy controls (normoalbuminuria: SMD=1.58, 95%CI, 0.59 to 2.56, P=0.002; microalbuminuria: SMD=2.57, 95%CI, 0.92 to 4.22, P=0.002; macroalbuminuria: SMD=2.69, 95%CI, 1.40 to 3.98, P=0.000). The Galbraith plot was used to detect the potential source of heterogeneity. However, we could not find the possible source of heterogeneity because it plotted too many studies as the outliers. In addition, we conducted subgroup analyses by region and type of DM. The results did not change in various subgroups, and the value of $I^2$ remained high in various subgroups, with the exception of one subgroup for studies based on population of Asia. What's more, serum YKL-40 levels increased with increasing severity of albuminuria among DM patients (macroalbuminuria vs normoalbuminuria: SMD=1.49, 95%CI, 0.28 to 2.71, P=0.016; macroalbuminuria vs microalbuminuria: SMD=0.93, 95%CI, 0.34 to 1.52, P=0.002).

Sensitivity analysis

We performed a sensitivity analysis by sequential omission of individual studies. When serum YKL-40 levels were compared between DM patients and healthy controls as well as DM patients with different degree of albuminuria and healthy controls, the pooled SMD were not materially altered. However, YKL-40 was not associated with GDM when the study by Xun Shengli et al. [36] was deleted.

Publication bias

Funnel plot and Egger's test were conducted to evaluate the potential publication bias. There was no obvious funnel plot asymmetry and all the P values of the Egger’s tests were over 0.05, suggesting that publication bias was not evident in our meta-analysis.
To our knowledge, this is the first systematic review and meta-analysis to assess the relationship between YKL-40 and DM. Our study indicate that DM patients have a significantly higher level of YKL-40 compared with healthy controls. In addition, YKL-40 concentrations are higher in DM patients with different degree of albuminuria than those in healthy controls and increase with increasing severity of albuminuria.

Diabetes mellitus is a complex group of metabolic diseases characterized by hyperglycemia and is a major public health problem throughout the world. Both of T1DM and T2DM are genetic diseases and influenced by environment. The genes responsible for T1DM are carried on chromosome 6p21 and take control of the immune system [46]. Many genes are relative to T2DM, but most of them have not been identified. Recently, inflammation is involved in the pathogenesis of DM. Previous study have found that long-term T1DM patients have a significantly higher level of CRP than healthy controls [47]. Besides, CRP is also higher in T2DM patients than in healthy controls [48]. But the role of inflammatory processes seems to be more important in the development of T2DM than T1DM. Some studies have indicated that inflammatory markers such as CRP and IL-6 are increased in healthy population who later developed T2DM [49, 50], suggesting that inflammation may occur ahead of the diagnosis of T2DM. Insulin resistance is common in T2DM and most patients with T2DM are obese, which itself can cause some degree of insulin resistance. Obesity, especially activation of adipose tissue, might enhance the release of inflammatory factors [51].

YKL-40, a new inflammatory marker, is related to both acute and chronic inflammation. Some studies have showed that levels of YKL-40 are increased in patients with purulent menigitis, rheumatoid arthritis, osteoarthritis, systemic lupus erythematous and inflammatory bowel disease [52, 53]. Obesity is related to increased macrophage infiltration of adipose tissue and plays an important role in the development of insulin resistance [54]. YKL-40 is possibly with relation to the insulin resistance based on the macrophage infiltration and adipose tissue [15]. All the evidences above indicate that YKL-40 might have a relationship with DM. And our study, with more strong power, confirm that patients with DM have significantly higher levels of YKL-40 compared with healthy controls. Some studies also show that YKL-40 levels are positively associated with diabetes duration [26,29] and glycated hemoglobin (HbA1c) [30-32,34,37]. It seems that YKL-40 might be a good metabolic indicator of DM. However, some find that there is no significant association between YKL-40 levels and HbA1c [26,28,29]. Therefore, studies with more DM patients need to be performed in the future.

The prevalence of GDM is increasing all over the world, of which the exact pathogenesis is not quietey understood. But many findings have showed that GDM patients have a trend of developing to T2MD. There are also some studies indicating that insulin resistance is an important pathophysiological contributor of GDM [55, 56]. Our present study find that the serum YKL-40 levels are higher in GDM patients than in healthy pregnancies. But when doing sensitivity analysis by sequential omission of individual studies, YKL-40 is not associated with GDM when the article by Xun Shengli et al. [36] is deleted. This might be related to the few studies included as well as the small sample sizes. Therefore, studies with more participants should be performed in the future.

There are three types of complications of DM, including macrovascular, microvascular and neurologic. Kidney is the most obviously involved organ in microvascular complications and urinary albumin is a sign of DN. Some studies have found a high prevalence of microalbuminuria in DM patients [57, 58]. The pathogenesis of DN is multiple, and inflammation seems to be a major mechanism. Interaction of metabolism and hemodynamics, which activates many inflammatory molecules and pathway, results in DN [59, 60]. In addition, vascular endothelial dysfunction is a major factor in the pathogenesis of diabetic micro-angiopathy [61]. And YKL-40 is expressed in the development of endothelial dysfunction, during the differentiation and maturation of CD14+ monocytes to CD14+, CD16+ macrophages [15]. YKL-40, as a marker of inflammation and endothelial dysfunction, is found associated with albuminuria in T2DM patients [62, 63]. Consistent with previous studies, we find that the levels of YKL-40 are higher in DM patients with different degree of albuminuria compared with healthy controls and the levels of YKL-40 are positively related with the severe degree of albuminuria.

Study limitations

Some limitations of this study should be mentioned. First, the heterogeneity is high and the major causes are not found by the Galbraith plot and subgroup analyses. Second, the criteria of normoalbuminuria, microalbuminuria and macroalbuminuria were different among the studies included in this meta-analysis. In some studies, urinary albumin excretion rate was used as classification criterion, but in others, albumin/creatinine was used. As thus, the results of our study are not stable enough.

Conclusion

In summary, our study demonstrates that DM patients have higher levels of YKL-40 compared with healthy controls. Additionally, levels of YKL-40 are significantly higher in DM patients with different degree of albuminuria than in the healthy controls and the levels of YKL-40 are positively related with the severe degree of albuminuria. Therefore, our current meta-analysis suggests that their sera should be detected for YKL-40, if DM, especially DN, is suspected in patients.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

All authors have contributed equally. All authors read and approved the final manuscript.

Funding
The authors have received no funding support regarding this study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

If the manuscript is accepted, we approve it for publication in Diabetology & Metabolic Syndrome.

Competing interests

None of the authors have any competing interests.

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**Tables**

Table 1. Characteristics of the studies included in this meta-analysis
| Study                  | Region    | Year | Type of DM | NO. of DM patients | NO. of healthy controls | Mean age of DM patients | Mean age of healthy controls | Diagnosis criteria                      |
|-----------------------|-----------|------|------------|--------------------|-------------------------|--------------------------|-------------------------------|---------------------------------------|
| Jian Li et al³¹        | China     | 2015 | GDM        | 35                 | 43                      | 29.3 ± 3.1               | 30.6 ± 3.8                    | ADA 2012                             |
| Rathcke CN et al²²     | Denmark   | 2005 | T2DM       | 87                 | 158                     | 54.2 (40–70)             | NA                           | National Diabetes Data Group 1979     |
| Thomsen SB et al²³     | Denmark   | 2010 | T2DM       | 45                 | 20                      | 54 (41-73)               | 50 (34-66)                    | NA                                    |
| Schaller G et al²⁴     | Austria   | 2010 | GDM        | 28                 | 30                      | 33 ± 6                   | 33 ± 4                        | ADA criteria for GDM 2004            |
| Sakamoto F et al²⁵     | Japan     | 2013 | T1DM       | 131                | 97                      | 24.7±5.9                 | 25.5±2.7                      | NA                                    |
| Rinnov AR et al²⁶      | Denmark   | 2015 | GDM        | 10                 | 8                       | 31.1 ± 5.6               | 28.1 ± 1.8                    | OGTT 2h GLU≥9.0mM                   |
| Abd El Dayem SM et al⁷ | Egypt     | 2015 | T1DM       | 62                 | 30                      | 16.32±1.52               | 16.13±2.63                    | NA                                    |
| Shiasi K et al²⁸       | Iran      | 2017 | T1DM       | 49                 | 43                      | 12.20 ± 3.86             | 10.95 ± 3.83                  | ADA                                   |
| Rekha Kumari D et al²⁹ | India     | 2015 | T2DM       | 30                 | 30                      | 44.4±2.7                 | 45.95±3.4                     | NA                                    |
| Song Wei et al³⁰       | China     | 2015 | T2DM       | 210                | 210                     | 58.29±5.94               | 59.98±7.53                    | NA                                    |
| Ye Kejun et al³¹       | China     | 2016 | GDM        | 50                 | 50                      | 27.2±3.4                 | 28.6±3.8                      | ADA 2005                             |
| Chen Qingfu et al³²    | China     | 2014 | T2DM       | 48                 | 45                      | NA                       | 48.1±13.7                     | WHO 1999                             |
| Li Peng et al³³        | China     | 2011 | T2DM       | 41                 | 40                      | 54.61±12.37              | 42.8±13.52                    | NA                                    |
| Lin Lijun et al³⁴      | China     | 2019 | T2DM       | 42                 | 40                      | NA                       | NA                            | NA                                    |
| Xun Shengli et al³⁵    | China     | 2017 | GDM        | 60                 | 20                      | 27.85±4.48               | 26.82±3.10                    | Obstetrics and gynecology [M]        |
| Yu Yeye et al³⁶        | China     | 2018 | T2DM       | 60                 | 60                      | 46.48±11.54              | 47.83±9.68                    | ADA 2007                             |
| Ren Lijue et al³⁷      | China     | 2019 | T2DM       | 30                 | 30                      | 57.20±10.30              | 54.5±10.44                    | WHO 1999                             |
| Rathcke CN et al³⁸     | Denmark   | 2009 | T1DM       | 58A/46B/45C        | 55                      | 55.6±10.8A/54±11.1B/49±9.6C | 50.5±10.9                    | NA                                    |
| Røndbjerg AK et al³⁹   | Denmark   | 2011 | T2DM       | 49A/35B/21C        | 20                      | 61.3±12.0A/60.1±11.7B/64±13.1C | 57.1±7.2                     | NA                                    |
| Lee JH et al⁴⁰         | South Korea| 2012 | T2DM       | 25A/25B/25C        | 22                      | 55.6±11.1A/57.0±11.6B/56.0±9.8C | 52.4±5.8                     | NA                                    |
| Han JY et al⁴¹         | China     | 2015 | T2DM       | 260A/246B/232C     | 210                     | 52.83±4.30A/53.93±4.56B/53.93±4.22C | 53.40±4.28                   | ADA 2007                             |
| Umapathy D et al⁴²     | India     | 2018 | T2DM       | 81A/73B/69C       | 83                      | 54.07±11.09A/55.1±10.9B/57.39±5.39C | 52.59±12.9                    | NA                                    |
| Zhu Huijing et al⁴³    | China     | 2015 | T2DM       | 23A/24B/23C       | 20                      | 63.00±13.76A/65.33±9.13B/66.35±7.84C | 62.0±11.16                   | ADA 2007                             |
| Authors         | Country | Year | Type | Mean/Range | N | Median/Range | Units |
|-----------------|---------|------|------|------------|---|--------------|-------|
| Wang Huan et al  | China   | 2015 | T2DM | 21\(^a\)/39\(^c\) | 30 | NA           | 68 ±8 |
| Yu Zhixuan et al | China   | 2017 | T2DM | 30\(^a\)/30\(^b\) | 30 | NA           | 55.45±7.36 |

A: DM patients with normoalbuminuria  
B: DM patients with microalbuminuria  
C: DM patients with macroalbuminuria  

a: mean/range  
b: median/range  

T1DM: type 1 diabetes mellitus  
T2DM: type 2 diabetes mellitus  
GDM: gestational diabetes mellitus  
ADA: American Diabetes Association  
WHO: World Health Organization  
ELISA: enzyme linked immunosorbent assay  
NA: not available