Research Article

Impact of Diabetic Ketoacidosis on Thyroid Function in Patients with Diabetes Mellitus

Yuling Xing,1,2 Jinhu Chen,1 Guangyao Song,1,3,4 Liying Zhao,1,2 and Huijuan Ma1,3,4

1Department of Endocrinology, Hebei General Hospital, Shijiazhuang 050017, China
2Graduate School of Hebei Medical University, Shijiazhuang 050017, China
3Hebei Key Laboratory of Metabolic Diseases, Hebei General Hospital, Shijiazhuang, Hebei 050051, China
4Department of Internal Medicine, Hebei Medical University, Shijiazhuang, Hebei 050017, China

Correspondence should be addressed to Huijuan Ma; huijuanma19@163.com

Received 11 May 2020; Revised 21 October 2020; Accepted 9 March 2021; Published 22 March 2021

Academic Editor: Magorzata Kotula Balak

Copyright © 2021 Yuling Xing et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Changes in thyroid function in diabetes patients who developed diabetic ketoacidosis (DKA) still need to be fully elucidated. The aim of this study was to systematically review available data on the relationship between thyroid function and DKA in diabetes patients who developed DKA.

Methods. Electronic databases (PubMed, EMBASE, Cochrane Library, and China Academic Journal Full-text Database (CNKI)) were searched systematically to search relevant literature before December 2020. The mean ± standard deviation and 95% confidence interval (95% CI) were used for evaluation, and sensitivity analysis was performed. Publication bias was estimated by funnel plot, Egger’s test, and Begger’s test.

Results. 29 studies were included in the meta-analysis, and the indicators (T4, T3, FT3, FT4, TSH, T3RU, and rT3) of patients with DKA were compared and analyzed. The results of this study showed that the levels of T4, T3, FT3, FT4, and TSH were decreased and the level of rT3 was increased in patients with DKA. Compared with after treatment, the levels of T4, T3, FT3, and FT4 in patients with DKA were decreased before treatment, while the levels of rT3 were increased, and there was no significant difference in changes of TSH. With the aggravation of DKA, the levels of T4, T3, FT3, and FT4 will further decrease, while the changes of TSH have no statistical difference.

Conclusion. Thyroid function changed in diabetic patients with DKA. It changed with the severity of DKA. This condition may be transient, preceding further recovery of DKA.

1. Introduction

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes. It is not only a sign of acute absolute insulin deficiency in type 1 diabetes mellitus (T1DM) but also increasingly seen in patients with type 2 diabetes mellitus. In patients with diabetes, ketoacidosis is caused by an acute decrease in insulin secretion and action in a severe insulin resistant state [1]. From 2002 to 2010 in the United States, about 30% of adolescents newly diagnosed with T1DM developed DKA [2]. The prevalence of DKA estimated at the onset of type 2 diabetes is quite different. African-American youth in Cincinnati and Arkansas was 41.4% [3] and 16% [4]. Statistics showed that thyroid dysfunction in people with diabetes is 2-3 times higher than people without diabetes [5]. The effect of nonthyroid diseases on thyroid function has been studied in anorexia nervosa, liver disease, kidney disease, and many other diseases [6]. Since the 1970s, it has been reported that acute disease can cause a variety of changes in the levels of thyroid hormones in patients who were not previously diagnosed with intrinsic thyroid disease. These changes are nonspecific and are related to the severity of the disease [7]. Diabetes can have a definite effect on thyroid function in various ways, leading to changes in the levels of thyroid hormones, including immunological mechanisms, cytokine pathways, and regulatory pathways of the hypothalamic-pituitary-thyroid axis [8]. When DKA occurred in patients with diabetes, the changes in thyroid function has received a great deal of attention from researchers. At present, there are
limited studies on the changes in levels of thyroid hormone in patients with DKA. DKA and its implication in the thyroid function has not been adequately reviewed. The study aimed to analyze the changes in the levels of thyroid hormones in patients with DKA and the relationship between the changes and the severity of DKA.

2. Materials and Methods

2.1. Literature Search Strategy. Diabetic ketoacidosis, related indicators reflecting thyroid function (free triiodothyronine (FT3), free thyroxine (FT4), triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), T3 resin uptake (T3RU), and reverse triiodothyronine (rT3)) as subject terms and keywords for joint search. All relevant literature published before December 2020 was searched in PubMed, EMBASE, Cochrane Library, and CNKI.

2.2. Inclusion Criteria. (1) The article related to patients with DKA; (2) involving the changes of thyroid function indicators in patients with DKA before and after treatment or between the diabetic patients with and without DKA and providing the exact sample size and data on various indicators of thyroid function; and (3) the diagnosis of diabetic ketoacidosis is clear [9].

2.3. Exclusion Criteria. (1) The data of literature are incomplete and the information is not enough to calculate the statistics of this study; (2) case reports; (3) repeated articles; and (4) studies limited to animals.

2.4. Literature Screening. Two researchers independently screened the literature, extracted data, and cross-checked. If there is a disagreement on the results, they would discuss it together or resolve it by a third senior researcher. In the study, data were extracted from the literature finally included in the meta-analysis using a premade data extraction table. The extracted content included the first author, year of publication, study area, sample size, mean ± standard deviation of thyroid function indicators, inclusion criteria, exclusion criteria, DKA diagnostic cutoff point, the determination method of thyroid hormone, therapeutic approach, and duration of treatment of DKA (Table 1).

2.5. Statistical Analysis. According to the requirements of meta-analysis, the data were sorted out, the database was established, the data were carefully checked, and the standardized mean difference (SMD) and 95% CI were used to quantitatively analyze the measurement data. I2 was used to quantitatively test the heterogeneity among the studies. If I2 ≤ 50%, it was considered that the heterogeneity was not statistically significant, and the fixed effect model was used to analyze; on the contrary, if I2 > 50%, the heterogeneity was considered to be statistically significant, and the random effect model was used to analyze. Sensitivity analysis was performed to ensure the stability of the meta-analysis results. Funnel plot and Egger’s test were used to evaluate publication bias, and p < 0.05 was considered as statistically significant, indicating that publication bias was not excluded. The trim-and-fill method was used to estimate the effect of publication bias on the interpretation of the results.

3. Result

3.1. Literature Search Results. 314 related studies were initially retrieved based on keywords and subject terms, and finally, 29 studies met the predetermined inclusion and exclusion criteria (Figure 1). 17 studies evaluated the changes of thyroid function before and after treatment in patients with DKA, 17 studies evaluated the difference of thyroid function between patients with diabetes with and without DKA, and 3 studies related to the changes of thyroid function with different severities of DKA. The relevant literature was published from 1978 to 2018 (Tables 1–3).

3.2. Meta-Analysis Results

3.2.1. Comparison of Thyroid Function between Patients with Diabetes with and without DKA. 15 studies involved the comparison of T4 between patients with diabetes with and without DKA, involving 751 patients with DKA and 817 patients with diabetes but without DKA; 16 studies involved the comparison of T3, involving 755 patients with DKA and 828 patients with diabetes but without DKA; 15 studies involved the comparison of FT4, involving 790 patients with DKA and 876 patients with diabetes but without DKA; 12 studies involved the comparison of FT3, involving 643 patients with DKA and 744 patients with diabetes but without DKA; 16 studies involved the comparison of TSH, involving 848 patients with diabetes and DKA and 981 patients with diabetes but without DKA; and 6 studies involved the comparison of rT3, involving 135 patients with DKA and 194 patients with diabetes but without DKA. The results showed that compared with patients with diabetes, patients with DKA had lower levels of T4, T3, FT4, and FT3 and higher level of rT3. The difference was statistically significant (T4: I2 = 83.9%, p < 0.01, Z = 7.2, p < 0.01, SMD = −1.030, 95% CI: −1.310 to −0.749; T3: I2 = 82.1%, p < 0.01, Z = 7.4, p < 0.01, SMD = −1.022, 95% CI: −1.292 to −0.751; FT4: I2 = 93.9%, p < 0.01, Z = 3.45, p < 0.01, SMD = −0.758, 95% CI: −1.189 to −0.327; FT3: I2 = 89.6%, p < 0.01, Z = 4.82, p < 0.01, SMD = −0.884, 95% CI: −1.243 to −0.524; rT3: I2 = 95.8%, p < 0.01, Z = 3.15, p < 0.01, SMD = 2.534, 95% CI: 0.956 to 4.112; TSH: I2 = 61.1%, p < 0.01, Z = 1.33, p = 0.185, SMD = −0.106, 95% CI: −0.261 to 0.05; Figure 2). There was no statistical difference in TSH between patients with diabetes with and without DKA. After sensitivity analysis, the result showed that TSH was significantly different (I2 = 42.6%, p < 0.05, Z = 2.01, p < 0.05, SMD = −0.138, 95% CI: −0.273 to −0.003 Figure 3). Therefore, patients with DKA have lower levels of T4, T3, FT4, FT3, and TSH and higher level of rT3. Egger’s test (T4, p = 0.861; FT4, p = 0.504; rT3, p = 0.445) showed that there was no obvious publication bias. Further analysis by the cut-and-fill method showed that the publication bias (T3, p = 0.043; FT3, p = 0.003; TSH, p = 0.003) did not affect the
| Author     | Diagnosis of DKA | Determination of thyroxine | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Therapeutic method             | Treatment time | Subgroup                                                                 |
|------------|------------------|-----------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------|----------------|--------------------------------------------------------------------------|
| Yan Zhao   | NA               | https://fanyi.baidu.com/    | There was no thyroid disease in the past, and no drugs affecting thyroid function were taken recently | NA                                                                                 | Untreated                     |                | Mild: pH < 7.3 or HCO₃⁻ < 15 mmol·L. Moderate: pH < 7.2 or HCO₃⁻ < 10 mmol·L. Severe: pH < 7.1 or HCO₃⁻ < 5 mmol·L. |
| Shixiong Zhang | Microparticle automatic chemiluminescence immunoassay analyzer (Beckman, USA) | There was no abnormal ECG and liver function.                                    |                                                                                    |                                                                                    | On the basis of routine diabetes treatment, the observation group was given routine treatment such as rehydration, removing inducement, maintaining acid-base and water-electrolyte balance, insulin, and other conventional treatment measures to correct ketoacidosis. According to the treatment principle of ketoacidosis, the treatment includes removing the inducement, replenishing fluid, applying insulin, and maintaining the acid-base balance of water and electrolyte. | 3 w                  |                             |
| Yunzhi Wang | Beckman microparticle automatic chemiluminescence immunoassay analyzer and corresponding kits provided by the company | The liver function and ECG were normal.                                         |                                                                                    |                                                                                    | Treatment method unknown       | 3 w            |                             |
| Yiping Wang | Beckman access 2 chemiluminescence immunoassay analyzer was used | There was no history of other acute and chronic diseases                         | Previous history of thyroid disease, taking thyroid function drugs Pregnant and lactating women | Treatment method unknown       | Unknown                      |                | Mild pH < 7.3 or HCO₃⁻ < 15 mmol·L. Moderate pH < 7.2 or HCO₃⁻ < 10 mmol·L. Severe pH < 7.1 or HCO₃⁻ < 5 mmol·L. |
| Author     | Diagnosis of DKA | Determination of thyroxine | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Therapeutic method                  | Treatment time | Subgroup |
|------------|------------------|---------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------|----------------|----------|
| Lan Wang   |                  | Primary thyroid diseases, no history of antithyroid drugs and thyroid surgery were excluded | Pregnant or lactating women, Patients with thyroid disease history and taking drugs affecting thyroid function, Patients with severe liver, heart, kidney, and connective tissue diseases, 40 patients with thyroid function analysis, Patients critical patients at admission, Patients without the thyroid function test and blood gas analysis on admission. | Untreated                          |                      |                |          |
| Yu Qiao    |                  | The symptoms of diabetes were aggravated, nausea, vomiting, dizziness, and other discomfort clinical manifestations, Dry skin, sunken orbit, rapid pulse, and other signs, Blood glucose >16 mmol/L, urine ketone body and urine sugar positive, blood gas analysis, anion gap increased, HCO₃⁻ decreased, and binding rate decreased (note: due to individual differences, some patients who have no obvious clinical symptoms or signs but meet the laboratory examination are also diagnosed with diabetic ketoacidosis) | Untreated                           |                      |                |          |
| Lianshan Piao |            | The immunoassay kit was provided by the Institute of Isotope, Chinese Academy of Atomic Energy | No pituitary, adrenal, and thyroid diseases were found, and no serious complications of chronic diabetes were found | After the treatment of high-dose rehydration and low-dose insulin continuous intravenous therapy, Urinary ketone body turned negative and carbonate ion returned to normal |                      |                |          |
| Li Luo     |                  | Siemens Centaur XP chemiluminescence immunoassay system | Other diseases that may affect thyroid function were excluded, and drugs affecting thyroid function were excluded | Untreated                           |                      |                |          |
| Author | Diagnosis of DKA | Determination of thyroxine | Inclusion criteria | Exclusion criteria | Therapeutic method | Treatment time | Subgroup |
|--------|-----------------|---------------------------|--------------------|--------------------|-------------------|----------------|----------|
| Shengbin Liu | Combined with serious heart, brain, liver, kidney, and other organ damage, thyroid disease, central nervous system systemic diseases, pregnant women having dopamine, glucocorticoid, androgen, and estrogen within 3 months may affect their own hormone levels, thus interfering with the drug use history of this study and having suffered from endocrine system diseases such as primary aldosteronism, and growth retardation | Untreated | Mild (pH $\geq 7.3$) | Moderate (7.3 $>$ pH $\geq 7.2$) | Severe (pH $< 7.2$) |
| Bin Liu | There was no history of thyroid disease, endocrine, glucocorticoid, sedative, furosemide, dopamine, and other drugs in the past, except lactation and pregnancy women. | Untreated | | | |
| Shaohui Huang | Microparticle automatic chemiluminescence analyzer (Beckman company, USA) | All the patients met the diagnostic criteria of diabetes established by the WHO | Abnormal ECG, abnormal liver function, the history of glucocorticoid, androgen, thyroid disease, infection, heart failure, and mental disease | Active treatment of primary disease, adequate fluid supplement, insulin, correction of water-electrolyte balance disorder, acid-base balance, and symptomatic treatment measures were adopted. | 3 w | |
| Author     | Diagnosis of DKA | Determination of thyroxine | Inclusion criteria | Exclusion criteria | Therapeutic method                                                                 | Treatment time | Subgroup |
|------------|------------------|----------------------------|--------------------|-------------------|-------------------------------------------------------------------------------------|----------------|----------|
| Rui Feng   |                  | Blood glucose was higher than 13.9 mmol/L, pH was less than 7.35, urine ketone was positive, anion gap was more than 16 mmol/L, and blood bicarbonate (HCO₃⁻) was less than 18 mmol/L | Enzyme linked immunosorbent assay | Ketoacidosis caused by acute cardiovascular and cerebrovascular diseases, gastrointestinal bleeding, major surgery, and pregnancy were excluded | All patients were treated with antibiotics to prevent infection, supplement electrolytes, and maintain body fluid balance. Patients with other basic diseases or complications were treated according to their condition. On this basis, the patients were treated with low-dose insulin intravenous drip, and the dose was 4–6 u/h | 24 h           |          |
| Wen Fan    |                  | Abbott i2000 chemiluminescence immunoassay system and its kit | Age ≥65 years. According to the diagnostic criteria issued by the American Diabetes Association in 2010. Informed consent in this study. | There are hypothyroidism diseases, such as graves’ disease and Hashimoto’s thyroiditis. Those who have recently taken drugs that affect thyroid function, such as estrogen, androgen, and glucocorticoid. Combined with acute viral hepatitis, hypoproteinemia, heart failure, kidney disease, infection, and so on. | Treatment method unknown | Unknown |          |
| Author         | Diagnosis of DKA                                   | Determination of thyroxine | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Therapeutic method                                                                 | Treatment time | Subgroup |
|---------------|--------------------------------------------------|----------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------|----------|
| Fuwan Ding    | Positive blood ketones                            | Radioimmunoassay           | Patients with the history of thyroid disease, severe heart, liver, kidney disease, and connective tissue were excluded. |                                                                                   | Resuscitation measures such as fluid rehydration, use of insulin to lower blood sugar, correction of water-electrolyte and acid-base imbalance, treatment of complications and comorbidities, and removal of ketosis inducements have stabilized the condition within 1–3 days. All patients did not use thyroxine preparations | 2 w            |          |
| Qing Chen     | Positive blood ketones                            | Chemiluminescence         | The history of thyroid diseases, patients taking drugs that affect thyroid function, severe heart, liver, kidney, and connective tissue disease, breast-feeding, and pregnant women |                                                                                   |                                                                                   | untreated      |          |
| Daoxiong Chen | Diabetes (according to the WHO's diagnostic criteria for diabetes) Positive blood ketones Blood gas analysis showed metabolic acidosis |                            | None of the observed patients had clinical manifestations of hyperthyroidism or hypothyroidism and no history of thyroid disease Without any history of thyroid problems, systemic diseases, and using drugs which interfere with thyroid function were enrolled into the study. |                                                                                   | Treatment method unknown                                                                 | 2 w            |          |
| Rashidi. H    |                                                  |                            |                                                                                   |                                                                                   | Treatment method unknown                                                                 | 2w             |          |
| Naeije. R. G  | Clinically euthyroid                               |                            |                                                                                   |                                                                                   | Untreated                                                                                     | 5 days         |          |
| Schienger. J. L |                                                |                            |                                                                                   |                                                                                   | Untreated                                                                                     |                |          |
| Author     | Diagnosis of DKA                                                                 | Determination of thyroxine | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Therapeutic method | Treatment time | Subgroup                  |
|------------|---------------------------------------------------------------------------------|---------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------|-----------------|---------------------------|
| Alexander  |                                                                                 | Double antibody RIA       | We limited the scope of our study to the effects of diabetes mellitus per se by   | Insulin                                                                          | 5 days             |
| 1983       |                                                                                 | commercial method (Abbott | excluding patients with other systemic illnesses                                  |                                                                                    |                    |                 |
|            |                                                                                 | Laboratories, North       |                                                                                    |                                                                                    |                    |                 |
|            |                                                                                 | Chicago, IL.)             |                                                                                    |                                                                                    |                    |                 |
| Miboluk,   |                                                                                 | Two different methods:   |                                                                                    | Insulin                                                                          | 5 days             |
| AA        |                                                                                 | radio immune assay (RIA)  |                                                                                    |                                                                                    |                    |                 |
|            |                                                                                 | and immune-radiometric    |                                                                                    |                                                                                    |                    |                 |
|            |                                                                                 | assay (IRMA)              |                                                                                    |                                                                                    |                    |                 |
| Lin. C. H  |                                                                                 | Serum glucose level 300mg/dl (16.7 mmol/L), a serum pH < 7.25 or serum bicarbonate < 15 mmol/L, and the presence of ketones in the urine. | Clinically euthyroid                                                             | Supportive treatment such as fluid infusion, acid-base imbalance correction, and electrolyte disturbance corintravenous insulin administered by an insulin pump at a rate of 4–6 U/h. | 3 days             |
| Jiao W     |                                                                                 | Blood glucose level >13.9 mmol/L, blood pH < 7.35, ketonuria positivity, anion gap (AG) > 16 mmol/L, and HCO$_3^-$ level < 18 mmol/L | Enzyme linked immunosorbent assay (ELISA)                                        | Patients with DKA induced by acute cardiovascular and cerebrovascular diseases, gastrointestinal haemorrhage, major surgery, or pregnancy were excluded | 24h                |                 |
| Author          | Diagnosis of DKA                                                                 | Determination of thyroxine                                  | Inclusion criteria                                                                 | Exclusion criteria                                                                                                                                                                                                 | Therapeutic method                                                                                       | Treatment time | Subgroup |
|-----------------|----------------------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------|----------|
| Hu, Y           | Blood glucose (BG) > 11 mmol/L, venous pH < 7.3, or bicarbonate < 15 mmol/L      | Automated chemiluminescent immunoassay system (Advia Centaur, Siemens, Munich, Germany). | Excluded patients with other endocrinological disorders, systemic illness, pituitary and thyroid disease, and a history of diabetes mellitus. Patients who had previously received any medication apart from insulin were also excluded. | After resolution of DKA, patients received multiple daily insulin injections, aspart (Novo Nordisk, Bagsvaerd, Denmark) immediately before each meal and glargine (Sanofi-Aventis, Paris, France) once daily at bedtime. The total daily insulin dose ranged from 0.6 to 1.5 IU/kg. | 7 days                                                                                                   |               |          |
| D. Glinoer, R   |                                                                                  | Serum FT 4 was measured using the kinetic FT4-I125 radioimmunoassay test system (kindly provided by Dr. G. Odstrchel, Corning Glass Works, Corning, NY, USA) |                                                                                     |                                                                                                                                                                                                                   | Low-dose insulin. Fluids and electrolytes                                                                 | 5 days         |          |
| F. Chiarelli    | pH < 7.2, HCO₃⁻ < 15 mmol/L, ketonuria: 4+                                      |                                                                                            | Without familiar or personal history for endocrinological diseases. No drugs (except insulin for the diabetics) were administered to the children. All the subjects examined were clinically euthyroid, and their weight did not exceed ideal body by more than 20%. | Untreated                                                                                                                                                                                                       | Untreated                                               |               |          |
| Alexander, 1982 | Hyperglycaemia above 14 mmol/L and pH < 7.3 or bicarbonate < 15 mmol/L in the presence of ketonuria | Double antibody RIA                                                                 |                                                                                     | Untreated                                                                                                                                                                                                      | Untreated                                               |               |          |
| Xin, Y          |                                                                                  |                                                                                            |                                                                                     | Untreated                                                                                                                                                                                                      | Untreated                                               |               |          |
Figure 1: The process of study selection.

Table 2: Comparison of thyroid function before and after treatment in patients with diabetes and DKA.

| Author                  | Year | Country   | DKA Mean | SD  | n  | After treatment Mean | SD  | n  |
|-------------------------|------|-----------|----------|-----|----|----------------------|-----|----|
| T4                      |      |           |          |     |    |                      |     |    |
| Daoxiong et al. [10]    | 1999 | China     | 79.38    | 19.13| 65 | 78.32                | 16.5| 65 |
| Glinoer et al. [11]     | 1980 | Belgium   | 6.2      | 0.6  | 17 | 9.7                  | 0.7 | 17 |
| Wang [12]               | 1999 | China     | 110.26   | 45.89| 62 | 118                  | 48.57| 62 |
| Piao and Li [13]        | 1999 | China     | 71.4     | 12.6 | 8  | 70.9                 | 12.3| 8  |
| Lin et al. [14]         | 2003 | China     | 4.39     | 3.03 | 76 | 7.72                 | 2.29| 76 |
| Mirboluk et al. [15]    | 2017 | Iran      | 3.18     | 1.4  | 16 | 5.17                 | 2.4 | 16 |
| Naeije et al. [16]      | 1978 | Germany   | 5.7      | 3.05 | 19 | 8.9                  | 2.18| 19 |
| Rashidi et al. [17]     | 2017 | Iran      | 7.6      | 2.53 | 20 | 8.41                 | 2.51| 20 |
| Huang and Su [18]       | 2016 | China     | 96.41    | 5.12 | 63 | 110.34               | 8.32| 63 |
| Fan [19]                | 2014 | China     | 95.83    | 7.54 | 81 | 102.54               | 8.04| 81 |
| Wang and Du [20]        | 2013 | China     | 96.3     | 23.1 | 69 | 109                  | 37.9| 69 |
| Zhang [21]              | 2014 | China     | 95.8     | 23.2 | 74 | 110.3                | 38.6| 74 |
| Ding and Ji [22]        | 2011 | China     | 96.29    | 20.1 | 30 | 102.3                | 20.55| 30 |
| Wang et al. [23]        | 2018 | China     | 65.68    | 20.32| 40 | 90.33                | 20.95| 40 |
| T3                      |      |           |          |     |    |                      |     |    |
| Daoxiong et al. [10]    | 1999 | China     | 1        | 0.24 | 65 | 1.16                 | 0.21| 65 |
| Wang [12]               | 1999 | China     | 1.26     | 0.46 | 62 | 2.29                 | 0.59| 62 |
| Piao and Li [13]        | 1999 | China     | 51.43    | 3.51 | 8  | 82.37                | 2.58| 8  |
| Lin et al. [14]         | 2003 | China     | 59.36    | 36.11| 76 | 140.63               | 48.24| 76 |
| Mirboluk et al. [15]    | 2017 | Iran      | 63.2     | 28.2 | 16 | 78.5                 | 26.2| 16 |
| Naeije et al. [16]      | 1978 | Germany   | 37       | 6    | 19 | 105                  | 9   | 19 |
| Rashidi et al. [17]     | 2017 | Iran      | 86       | 25.7 | 20 | 161.25               | 38  | 20 |
| Huang and Su [18]       | 2016 | China     | 1.34     | 0.25 | 63 | 1.65                 | 0.31| 63 |
| Fan [19]                | 2014 | China     | 1.38     | 0.12 | 81 | 1.45                 | 0.21| 81 |
| Wang and Du [20]        | 2013 | China     | 1.38     | 0.23 | 69 | 1.52                 | 0.39| 69 |
| Zhang [21]              | 2014 | China     | 1.39     | 0.24 | 74 | 1.53                 | 0.41| 74 |
| Ding and Ji [22]        | 2011 | China     | 0.75     | 0.2  | 30 | 1.68                 | 0.33| 30 |
| Wang et al. [23]        | 2018 | China     | 0.84     | 0.3  | 40 | 1.55                 | 0.33| 40 |
| FT4                     |      |           |          |     |    |                      |     |    |
| Daoxiong et al. [10]    | 1999 | China     | 14.21    | 2.8  | 65 | 13.8                 | 2.5 | 65 |
| Glinoer et al. [11]     | 1980 | Belgium   | 1.4      | 0.1  | 17 | 1.7                  | 0.1 | 17 |
| Hu et al. [24]          | 2015 | China     | 11.38    | 3.58 | 40 | 15.57                | 2.92| 40 |
| Jiao et al. [25]        | 2016 | China     | 11.61    | 3.53 | 120| 14.23                | 3.01| 120|
| Lin et al. [14]         | 2003 | China     | 0.59     | 0.36 | 76 | 1.29                 | 0.32| 76 |
| Rashidi et al. [17]     | 2017 | Iran      | 1.07     | 0.43 | 20 | 1.58                 | 0.62| 20 |
estimator. It is more certain that the effect estimates obtained in the meta-analysis are effective. The funnel plot is shown in Figure 4.

3.2.2. Comparison of Thyroid Function before and after Treatment in Patients with Diabetes and DKA. 14 studies involved the comparison of T4 before and after treatment in patients with DKA, including a total of 640 patients with DKA; 13 studies involved the comparison of T3 before and after treatment, including a total of 623 patients with DKA; 13 studies involved the comparison of FT4 before and after treatment, including a total of 755 patients with DKA; 10 studies involved the comparison of FT3 before and after treatment, including a total of 599 patients with DKA; 15 studies involved the comparison of TSH before and after treatment, including a total of 832 patients with DKA; 5 studies involved the comparison of T3RU before and after treatment, including a total of 148 patients with DKA; and 3 studies involved the comparison of rT3 before and after treatment, including a total of 114 patients with DKA. The results showed that patients with DKA had lower levels of T4, T3, FT4, and FT3 and higher level of rT3 compared with after treatment. The difference

| Author          | Year | Country | DKA | After treatment |
|-----------------|------|---------|-----|----------------|
| Feng [26]       | 2014 | China   | 11.62 | 14.24 |
| Huang and Su [18]| 2016 | China   | 13.21 | 15.28 |
| Fan [19]        | 2014 | China   | 13.44 | 14.02 |
| Wang and Du [20]| 2013 | China   | 13    | 14.2  |
| Zhang [21]      | 2014 | China   | 13.2  | 14.6  |
| Ding and Ji [22]| 2011 | China   | 13.32 | 13.92 |
| Wang et al. [23]| 2018 | China   | 11.91 | 14.26 |

| FT3             |
|-----------------|
| Daoxiong et al. [10] | 1999 | China | 2.48  | 3.38 |
| Hu et al. [24]   | 2015 | China | 2.63  | 4.77 |
| Jiao et al. [25] | 2016 | China | 2.85  | 3.98 |
| Rashidi et al. [17] | 2017 | Iran  | 147   | 3.8  |
| Feng [26]        | 2014 | China | 2.87  | 3.96 |
| Fan [19]         | 2014 | China | 3.54  | 3.6  |
| Wang and Du [20] | 2013 | China | 3.54  | 3.69 |
| Zhang [21]       | 2014 | China | 3.55  | 3.65 |
| Ding and Ji [22] | 2011 | China | 2.21  | 4.08 |
| Wang et al. [23] | 2018 | China | 2.71  | 4.48 |

| TSH             |
|-----------------|
| Daoxiong et al. [10] | 1999 | China | 1.95  | 1.74 |
| Glinser et al. [11] | 1980 | Belgium | 29  | 74  |
| Hu et al. [24]   | 2015 | China | 1.77  | 2.17 |
| Jiao et al. [25] | 2016 | China | 1.8   | 2.33 |
| Wang [12]        | 1999 | China | 2.94  | 3.21 |
| Lin et al. [14]  | 2003 | China | 1.37  | 2.03 |
| Mirboluk et al. [15] | 2017 | Iran  | 1.85  | 1.79 |
| Naeije et al. [16] | 1978 | Germany | 1.9  | 2.6  |
| Feng [26]        | 2014 | China | 1.82  | 2.32 |
| Huang and Su [18]| 2016 | China | 4.48  | 4.09 |
| Fan [19]         | 2014 | China | 4.08  | 3.89 |
| Wang and Du [20] | 2013 | China | 4.47  | 4.12 |
| Zhang [21]       | 2014 | China | 4.49  | 4.24 |
| Ding and Ji [22] | 2011 | China | 1.33  | 1.56 |
| Wang et al. [23] | 2018 | China | 1.75  | 2.63 |

| T3RU            |
|-----------------|
| Glinser et al. [11] | 1980 | Belgium | 31.1 | 29.4 |
| Lin et al. [14]  | 2003 | China   | 33.33 | 32.07|
| Mirboluk et al. [15] | 2017 | Iran   | 32.4 | 32.1 |
| Naeije et al. [16] | 1978 | Germany | 31.5 | 30.8 |
| Rashidi et al. [17] | 2017 | Iran   | 1.7  | 1.7  |

| rT3             |
|-----------------|
| Ding and Ji [22] | 2011 | China  | 1.3  | 0.81 |
| Naeije et al. [16] | 1978 | Germany | 40  | 26.15|
| Daoxiong et al. [10] | 1999 | China  | 0.78 | 0.49 |
Table 3: Comparison of thyroid function between patients with diabetes with and without DKA.

| Author            | Year | Country     | DKA          | Control       |
|-------------------|------|-------------|--------------|---------------|
|                   |      |             | Mean  SD  n  | Mean  SD  n   |
| T4                |      |             | T4           | T4            |
| Alexander et al.  | 1983 | United States| 5.5 0.6 12  | 8.7 0.6 6    |
| Chiarelli et al.  | 1989 | Germany     | 58.22 15.02 16 | 74.04 23.07 45 |
| Daoxiong et al.   | 1999 | China       | 79.38 19.13 65 | 94.6 18.12 60 |
| Li et al.         | 2012 | China       | 82.4289 22.6743 38 | 109.094 17.9297 36 |
| Lin et al.        | 2003 | China       | 4.39 3.03 76 | 7.6 1.86 62 |
| Schienger et al.  | 1982 | Germany     | 7.6 0.3 8   | 7.8 0.5 8    |
| Huang and Su      | 2016 | China       | 96.41 5.12 63 | 107.52 8.12 62 |
| Fan               | 2014 | China       | 95.83 7.54 81 | 7.6 1.86 62 |
| Zhao et al.       | 2012 | China       | 5.65 2.8 91 | 9.28 2.85 110 |
| Wang and Du       | 2013 | China       | 96.3 23.1 69 | 114.8 41.2 74 |
| Qiao              | 2012 | China       | 5.95 1.57 40 | 7.8 1.67 40  |
| S. Liu            | 2016 | China       | 92.9 18.78 23 | 114.09 18.83 31 |
| Chen et al.       | 2016 | China       | 102.46 22.73 65 | 107.28 23.28 65 |
| Zhang             | 2014 | China       | 95.8 23.2 74 | 165 42.3 84  |
| Ding and Ji       | 2011 | China       | 96.29 20.1 30 | 100.3 20.33 30 |
| T3                |      |             | T3           | T3            |
| Alexander et al.  | 1983 | United States| 49.9 7.3 12  | 88 8 6       |
| Chiarelli et al.  | 1982 | United States| 49 9 4 103 | 7 11        |
| Daoxiong et al.   | 1989 | Germany     | 1.04 0.36 16 | 1.39 0.42 45 |
| Li et al.         | 2012 | China       | 1.5482 0.4371 38 | 1.9497 0.2762 36 |
| Lin et al.        | 2003 | China       | 59.36 36.11 76 | 91.4 31.85 62 |
| Schienger et al.  | 1982 | Germany     | 124 14 8 | 115 6 8     |
| Huang and Su      | 2016 | China       | 1.34 0.25 63 | 1.52 0.31 62 |
| Fan               | 2014 | China       | 1.38 0.12 81 | 1.55 0.21 94 |
| Zhao et al.       | 2012 | China       | 0.54 0.51 91 | 1.02 0.38 110 |
| Wang and Du       | 2013 | China       | 1.38 0.23 69 | 1.59 0.47 74 |
| Qiao              | 2012 | China       | 0.75 0.22 40 | 1.05 0.21 40 |
| S. Liu            | 2016 | China       | 1.6 0.41 23 | 1.85 0.33 31 |
| Chen et al.       | 2016 | China       | 1.53 0.24 65 | 1.72 0.27 65 |
| Zhang             | 2014 | China       | 1.39 0.24 74 | 1.61 0.45 84 |
| Ding and Ji       | 2011 | China       | 0.75 0.2 30 | 1.72 0.31 30 |
| FT4               |      |             | FT4          | FT4           |
| Liu               | 2012 | China       | 0.84 0.21 20 | 1.15 0.38 60 |
| Chiarelli et al.  | 1989 | Germany     | 10.24 2.94 16 | 11.55 3.62 45 |
| Daoxiong et al.   | 1999 | China       | 14.21 2.8 65 | 12.13 2.88 60 |
| Qiu et al.        | 2018 | China       | 12.4 4.89 75 | 15.97 3.08 39 |
| Lin et al.        | 2003 | China       | 0.59 0.36 76 | 1.18 0.4 62 |
| Huang and Su      | 2016 | China       | 13.21 0.24 63 | 14.29 0.31 62 |
| Fan               | 2014 | China       | 13.44 0.95 81 | 14.35 0.36 94 |
| Xin et al.        | 2010 | China       | 12.99 7.3 85 | 15.34 3.97 118 |
| Wang and Du       | 2013 | China       | 13 2.3 69 | 14 1.2 74 |
| Qiao              | 2012 | China       | 1.13 0.26 40 | 1.21 0.17 40 |
| S. Liu            | 2016 | China       | 10.76 2.1 23 | 12.12 1.46 31 |
| Chen et al.       | 2016 | China       | 11.86 2.57 65 | 12.51 2.78 65 |
| Zhang             | 2014 | China       | 13.2 2.4 74 | 14.9 1.3 84 |
| Ding and Ji       | 2011 | China       | 13.32 2.52 30 | 14.31 4.01 30 |
| Schienger et al.  | 1982 | Germany     | 2.3 0.29 8 | 2.2 0.29 8 |
| FT3               |      |             | FT3          | FT3           |
| Liu               | 2012 | China       | 3.96 0.92 20 | 5.83 1.96 60 |
| Chiarelli et al.  | 1989 | Germany     | 2.05 1.01 16 | 2.35 0.71 45 |
| Daoxiong et al.   | 1999 | China       | 2.48 0.9 65 | 3.46 0.89 60 |
| Qiu et al.        | 2018 | China       | 2.47 0.74 75 | 3.07 0.84 39 |
| Fan               | 2014 | China       | 3.54 0.23 81 | 3.69 0.44 94 |
| Xin et al.        | 2010 | China       | 2.61 1.93 85 | 3.31 1.27 118 |
| Wang and Du       | 2013 | China       | 3.54 0.53 69 | 3.65 0.49 74 |
| Qiao              | 2012 | China       | 2.21 0.61 40 | 2.85 0.3 40 |
was statistically significant (T4: I2 = 86.2%, p < 0.01, Z = 4.50, p < 0.01, SMD = −0.742, 95% CI: −1.066 to 0.419; T3: I2 = 93%, p < 0.01, Z = 6.04, p < 0.01, SMD = −1.538, 95% CI: −2.037 to −1.039; FT4: I2 = 93.8%, p < 0.01, Z = 4.52, p < 0.01, SMD = −1.035, 95% CI: −1.483 to −0.856; FT3: I2 = 95.9%, p < 0.01, Z = 3.68, p < 0.01, SMD = −1.258, 95% CI: −1.926 to −0.589; rT3: I2 = 94.7%, p < 0.01, Z = 2.57, p = 0.01, SMD = 1.967, 95% CI: 0.467 to 3.467 Figure 5). There was no significant difference in TSH and T3RU in patients with DKA before and after treatment. Egger’s test (T4, p = 0.566; T3RU, p = 0.243; FT4, p = 0.175; FT3, p = 0.988; TSH, p = 0.599; rT3, p = 0.236) showed that there was no obvious publication bias, further analysis by the trim-and-fill method showed that the publication bias (T3, p = 0.006) did not affect the estimator, and it was more certain that the effect estimation obtained in the meta-analysis was effective. The funnel plot is shown in Figure 6.

3.2.3. Comparison of Severity of DKA and Thyroid Function in Patients with Diabetes and DKA. Three studies involved the comparison of the severity of DKA with thyroid function. The results showed that as the degree of DKA aggravated, the levels of T4, T3, FT4, and FT3 further decreased. The level of TSH increased with the aggravation of DKA, but it was not statistically significant (Figure 7).

4. Discussion

This meta-analysis study showed that the levels of T4, T3, FT3, FT4, and TSH were lower and the level of rT3 was higher in patients with DKA compared with patients with diabetes but not DKA. The levels of T4, T3, FT3, and FT4 were lower and the level of rT3 was higher compared with after treatment in patients with diabetes and DKA. As the aggravation of DKA, the levels of T4, T3, FT3, and FT4 would further decrease, but there was no statistical difference in the change of TSH.

DKA can affect the function of the hypothalamus-pituitary-thyroid axis directly or indirectly due to various factors such as relatively insufficient insulin secretion and metabolic disorders, thus affecting thyroid function [38]. Picioni et al. found that large blood glucose fluctuations trigger the production of nitrotyrosine and induce the expression of adhesion molecules and IL-6 [39]. The release of a large number of cytokines acted on the hypothalamus-pituitary-thyroid axis through a variety of ways, which can also affect the synthesis, secretion, metabolism, and feedback of thyroid hormones [40]. An increase in cytokines such as IL-6 synchronizing with a low T3 level is often observed which may cause hypothalamic involvement [41]. The body’s caloric intake is seriously insufficient in patients with DKA, leading to hypoxia in the cells, which reduced the biological activity of 5′-deiodinase, resulting in a significant

### Table 3: Continued.

| Author | Year | Country | DKA | Control |
|--------|------|---------|-----|---------|
| Mean   | SD   | n       | Mean | SD      | n     |
| S. Liu [33] | 2016 | China   | 4.32 | 0.66 | 23 | 4.95 | 0.63 | 31 |
| Chen et al. [34] | 2016 | China   | 3.95 | 1.14 | 65 | 4.46 | 1.17 | 65 |
| Zhang [21] | 2014 | China   | 3.55 | 0.54 | 74 | 3.64 | 0.51 | 84 |
| Ding and Ji [22] | 2011 | China   | 2.21 | 0.41 | 30 | 4.25 | 0.41 | 30 |
| Alexander et al. [27] | 1983 | The United States | 3.4 | 0.9 | 12 | 4.4 | 0.7 | 31 |
| Liu [35] | 2012 | China   | 0.83 | 0.73 | 20 | 1.25 | 1.19 | 60 |
| Chiarelli et al.[28] | 1989 | Germany | 1.66 | 0.69 | 16 | 2.56 | 1.27 | 45 |
| Daoxiong et al. [10] | 1999 | China   | 1.95 | 0.85 | 65 | 2.02 | 0.96 | 60 |
| Li et al. [29] | 2012 | China   | 1.5092 | 1.3515 | 38 | 2.0213 | 0.9604 | 36 |
| Lin et al. [14] | 2010 | China   | 1.37 | 1.46 | 76 | 1.6 | 1.01 | 62 |
| Huang and Su [18] | 2016 | China   | 4.48 | 1.24 | 63 | 4.46 | 1.31 | 62 |
| Fan [19] | 2014 | China   | 4.08 | 0.28 | 81 | 3.95 | 0.23 | 94 |
| Xin et al. [37] | 2010 | China   | 1.7 | 1.48 | 85 | 1.66 | 0.77 | 118 |
| Zhao et al. [31] | 2012 | China   | 2.49 | 2.73 | 91 | 2.45 | 2.01 | 110 |
| Wang and Du [20] | 2013 | China   | 4.47 | 1.59 | 69 | 4.23 | 1.53 | 74 |
| Qiao [32] | 2012 | China   | 1.38 | 0.86 | 40 | 1.82 | 0.88 | 60 |
| S. Liu [33] | 2012 | China   | 3.15 | 0.58 | 65 | 3.17 | 0.71 | 65 |
| Zhang [21] | 2014 | China   | 4.49 | 1.61 | 74 | 4.23 | 1.5 | 84 |
| Ding and Ji [22] | 2011 | China   | 1.33 | 0.76 | 30 | 1.43 | 0.82 | 30 |

**rT3**

| Author | Year | Country | DKA | Control |
|--------|------|---------|-----|---------|
| Mean   | SD   | n       | Mean | SD      | n     |
| Ding and Ji [22] | 2011 | China   | 1.3 | 0.3 | 30 | 0.83 | 0.17 | 30 |
| Chiarelli et al.[28] | 1989 | Germany | 0.23 | 0.1 | 16 | 0.22 | 0.07 | 45 |
| Alexander et al. [27] | 1983 | The United States | 57.8 | 25.3 | 12 | 35.7 | 8.3 | 6 |
| Schienger,J.B1982 | Germany | 25.2 | 3.4 | 8 | 23.5 | 5.4 | 8 |
| Alexander et al. [6] | 1982 | The United States | 83 | 2 | 4 | 33 | 2 | 35 |
| Daoxiong et al. [10] | 1999 | China   | 0.78 | 0.09 | 65 | 0.52 | 0.1 | 70 |
### T4

| Study ID                  | SMD (95% CI)        | Weight % |
|--------------------------|---------------------|----------|
| Alexander, C. M.1983, 1983 | -1.68 (-2.82, -0.54)| 3.53     |
| Chiarelli,F, 1989        | -0.74 (-1.33, -0.16)| 6.19     |
| Daomiong Chen, 1999      | -0.82 (-1.17, -0.47)| 7.48     |
| Li Luo, 2012             | -1.30 (-1.80, -0.80)| 6.66     |
| Lin.H.C, 2003            | -1.25 (-1.61, -0.88)| 7.40     |
| Schienger,JB, 1982       | -0.17 (-1.15, 0.81) | 4.16     |
| Shixiong Zhang, 2014     | -1.64 (-2.05, -1.23)| 7.20     |
| Wen Fan, 2014            | -1.26 (-1.59, -0.94)| 7.61     |
| Yan Zhao, 2012           | -1.28 (-1.59, -0.98)| 7.70     |
| Yunzhii Wang, 2013       | -0.55 (-0.88, -0.21)| 7.57     |
| Yu Qiao, 2012            | -1.14 (-1.61, -0.67)| 6.83     |
| Shengbin Liu, 2016       | -1.13 (-1.71, -0.55)| 6.21     |
| Qing Chen, 2016          | -0.21 (-0.55, 0.14) | 7.51     |
| Shixiong Zhang, 2014     | -1.99 (-2.38, -1.61)| 7.32     |
| FuwanDing, 2011          | -0.20 (-0.71, 0.31) | 6.64     |
| Overall (I² = 83.9%, p = 0.000) | -1.03 (-1.31, -0.75)| 100.00   |

Note: Weights are from random effects analysis.
| Study ID              | SMD (95% CI)              | Weight (%) |
|----------------------|---------------------------|------------|
| Bin Liu, 2012       | -0.90 (-1.44, -0.37)     | 6.54       |
| Chiarelli, F, 1989  | -0.38 (-0.95, 0.20)      | 6.44       |
| Daoxiong Chen, 1999 | 0.73 (0.38, 1.08)        | 6.94       |
| Junlin Qiu, 2018    | -0.82 (-1.22, -0.42)     | 6.87       |
| Lin, H.C, 2003      | -1.56 (-1.94, -1.18)     | 6.87       |
| Shaohui Huang, 2016 | -3.90 (-4.50, -3.30)     | 6.37       |
| Wen Fan, 2014       | -1.30 (-1.63, -0.98)     | 6.98       |
| Xin, Y, 2010        | -0.24 (-0.70, -0.14)     | 7.05       |
| Yunzhi Wang, 2013   | -0.55 (-0.88, -0.22)     | 6.96       |
| Yu Qiao, 2012       | -0.36 (-0.81, 0.08)      | 6.75       |
| Shengbin Liu, 2016  | -0.77 (-1.33, -0.21)     | 6.67       |
| Qing Chen, 2016     | -0.24 (-0.59, 0.10)      | 6.95       |
| Shixiong Zhang, 2014| -0.90 (-1.22, -0.57)     | 6.98       |
| Fuwan Ding, 2011    | -0.30 (-0.80, 0.21)      | 6.60       |
| Schienger, I.B, 1982| 0.35 (-0.64, 1.34)       | 5.26       |
| Overall (I-squared = 93.9%, p = 0.000) | -0.76 (-1.19, -0.33) | 100.00    |

Note: Weights are from random effects analysis

---

| Study ID              | SMD (95% CI)              | Weight (%) |
|----------------------|---------------------------|------------|
| Bin Liu, 2012       | -1.07 (-1.61, -0.53)     | 7.97       |
| Chiarelli, F, 1989  | -0.38 (-0.95, 0.20)      | 7.79       |
| Daoxiong Chen, 1999 | -1.10 (-1.46, -0.73)     | 8.85       |
| Junlin Qiu, 2018    | -0.75 (-1.15, -0.35)     | 8.69       |
| Wen Fan, 2014       | -0.42 (-0.72, -0.12)     | 9.11       |
| Xin, Y, 2010        | -0.44 (-0.73, -0.16)     | 9.18       |
| Yunzhi Wang, 2013   | -0.22 (-0.54, 0.11)      | 9.00       |
| Yu Qiao, 2012       | -1.33 (-1.82, -0.85)     | 8.26       |
| Shengbin Liu, 2016  | -0.98 (-1.55, -0.41)     | 7.81       |
| Qing Chen, 2016     | -0.44 (-0.79, -0.09)     | 8.92       |
| Shixiong Zhang, 2014| -0.17 (-0.48, 0.14)      | 9.06       |
| Fuwan Ding, 2011    | -4.98 (-6.01, -3.94)     | 5.37       |
| Overall (I-squared = 89.6%, p = 0.000) | -0.88 (-1.24, -0.52) | 100.00    |

Note: Weights are from random effects analysis

Figure 2: Continued.
Figure 2: Forest plot of T4, T3, FT4, FT3, rT3, and TSH compared with patients with DKA and diabetes.
Note: Weights are from random effects analysis

Overall ($I^2 = 42.6\%, p = 0.041$)

| Study ID                  | SMD (95% CI)        | Weight (%) |
|---------------------------|---------------------|------------|
| Alexander, C. M. 1983, 1983 | $-0.36 (-1.35, 0.63)$ | 1.67       |
| Bin Liu, 2012             | $-0.39 (-0.90, 0.13)$ | 4.82       |
| Chiarelli.F, 1989         | $-0.78 (-1.37, -0.19)$ | 3.99       |
| Daoxiong Chen, 1999       | $-0.08 (-0.41, 0.26)$ | 8.13       |
| Li Luo, 2012              | $-0.43 (-0.90, 0.03)$ | 5.64       |
| Lin.H.C, 2003             | $-0.18 (-0.52, 0.16)$ | 8.17       |
| Shaohui Huang, 2016       | $0.02 (-0.33, 0.37)$  | 7.82       |
| Xin.Y, 2010               | $0.04 (-0.24, 0.31)$  | 9.71       |
| Yan Zhao, 2012            | $0.02 (-0.26, 0.29)$  | 9.74       |
| Yunzhi Wang, 2013         | $0.15 (-0.17, 0.48)$  | 8.36       |
| Yu Qiao, 2012             | $-0.51 (-0.95, -0.06)$ | 5.90       |
| Shengbin Liu, 2016        | $-0.74 (-1.30, -0.18)$ | 4.32       |
| Qing Chen, 2016           | $-0.03 (-0.37, 0.31)$ | 7.98       |
| Shixiong Zhang, 2014      | $0.17 (-0.15, 0.48)$  | 8.76       |
| FuwanDing, 2011           | $-0.13 (-0.63, 0.38)$ | 4.96       |
| Overall ($I^2 = 42.6\%, p = 0.041$) | $-0.14 (-0.27, -0.00)$ | 100.00    |

Note: Weights are from random effects analysis

Figure 3: Sensitivity analysis of TSH.
reduction in the conversion of T4 to T3, and a significant reduction in the levels and activity of thyroid hormones [42]. Studies have shown that T1DM and thyroid diseases have a common genetic basis [43]. There is a significant positive correlation between serum TSH and antithyroid antibodies (TRAb, TPOAb, and TGAb) in patients with T2DM, suggesting that abnormal thyroid function in patients with T2DM is autoimmune-mediated pathogenesis [44].

Studies also found that the severity of impaired hypothalamus-hypophyseal-thyroid regulation seems to be related to the degree of metabolic disorders regardless of the presence of antithyroid antibodies [45]. Previous studies have shown that the levels of serum T3 and T4 are related to the severity of the disease [46, 47]. Balsamo et al. showed that changes in hormone levels are usually related to the severity of metabolic disorders, among which thyroid function is one of the most serious disorders. The hypothalamic-pituitary-thyroid axis showed variable damage, which was defined as nonthyroid disease syndrome (NTIS) [45]. The relationship between the degree of NTIS and the severity of metabolic disorders has previously been reported in adults and children [48–51]. NTIS is now more commonly used to describe a typical change in the serum levels of thyroid-related hormones that may occur after an acute or chronic disease not caused by intrinsic abnormalities in thyroid function. Changes in the hypothalamic-pituitary-thyroid axis also occur in diseases, usually associated with low levels of T3, which gave rise to the term “low T3 syndrome” [52].

It was now well known that most circulating T3 and almost all rT3 came from the peripheral deiodination of T4 [53, 54]. Pittman et al. found that DKA played a certain role in the peripheral transformation of T4 [55]. The moderate decrease in serum T4 observed in patients with DKA has been described previously, which was corrected after treatment, and it seemed to be due to acquired deficiency of T4 binding to serum protein [56]. The factors of dietary, especially carbohydrates, played an important role in the regulation of T3 [57, 58]. The presence of carbohydrate deprivation in DKA seemed to rapidly inhibit the deiodination of T4 by type 1 iodothyronine-deiodinase in the liver, thereby inhibiting the production of T3 and preventing the metabolism of rT3 [59]. Carbohydrate deprivation will lead to a decrease in basal metabolic rate. The decrease in thyroid hormones is represented the body’s remaining adaptive response to calories and protein by inducing hypothyroidism theoretically [60]. It was reported that the average level of rT3 was increased in patients with insulin-dependent diabetes, and the average metabolic clearance rate of rT3 is decreased [55, 61]. The result of Pittman CS et al. suggested that T4 monodeiodination of both phenyl rings was significantly impaired in uncontrolled diabetes, and they
Note: Weights are from random effects analysis

| Study ID            | SMD (95% CI)       | Weight (%) |
|---------------------|--------------------|------------|
| Rashidi.H, 2017     | -0.86 (-1.18, -0.54) | 8.08       |
| Wen Fan, 2014       | -0.40 (-0.74, -0.07)  | 8.02       |
| Yunzhi Wang, 2013   | -0.46 (-0.78, -0.13)  | 8.06       |
| Shixiong Zhang, 2014| -0.30 (-0.80, 0.21)   | 7.21       |
| FuwanDing, 2011     | -0.19 (-1.67, -0.72)  | 7.37       |
| Overall (I-squared = 86.2%, p = 0.000) | -0.74 (-1.07, -0.42)  | 100.00     |

Note: Weights are from random effects analysis

---

| Study ID            | SMD (95% CI)       | Weight (%) |
|---------------------|--------------------|------------|
| Rashidi.H, 2017     | -0.63 (-1.06, 0.20)  | 8.68       |
| Wen Fan, 2014       | -0.57 (-1.07, 0.35)  | 8.51       |
| Yunzhi Wang, 2013   | -0.46 (-0.79, 0.00)  | 8.72       |
| Shixiong Zhang, 2014| -0.23 (-0.80, 0.08)  | 8.74       |
| FuwanDing, 2011     | 0.00 (-0.24, 0.24)   | 8.36       |
| Overall (I-squared = 93.0%, p = 0.000) | -0.13 (-0.47, 0.21)  | 100.00     |

Note: Weights are from random effects analysis

---

(a)

Figure 5: Continued.
Note: Weights are from random effects analysis
Overall ($I^2$ = 93.8%, $p$ = 0.000)
Lin.H.C, 2003
Shixiong Zhang, 2014
Wen Fan, 2014
Glinoer.D, 1980
Rashidi.H, 2017
Rui Feng, 2014
Shaohui Huang, 2016
Yiping Wang, 2018

| Study ID             | SMD (95% CI)   | Weight (%) |
|----------------------|----------------|------------|
| Daoxiong Chen, 1999 | 0.15 (−0.19, 0.50) | 7.97       |
| Glinoer.D, 1980     | −0.73 (−1.42, −0.03) | 6.97       |
| Hu.Y.Y, 2015        | −1.28 (−1.76, −0.80) | 7.63       |
| Jiao.W, 2016        | −0.80 (−1.06, −0.54) | 8.13       |
| Lin.H.C, 2003       | −2.06 (−2.45, −1.66) | 7.86       |
| Rashidi.H, 2017     | −0.96 (−1.61, −0.30) | 7.10       |
| Rui Feng, 2014      | −0.80 (−1.17, −0.43) | 7.91       |
| Shaohui Huang, 2016 | −4.22 (−4.86, −3.59) | 7.18       |
| Wen Fan, 2014       | −0.53 (−0.85, −0.22) | 8.04       |
| Yunzhi Wang, 2013   | −0.68 (−1.02, −0.33) | 7.98       |
| Shixiong Zhang, 2014| −0.75 (−1.08, −0.42) | 8.00       |
| FuwanDing, 2011     | −0.18 (−0.69, 0.33)  | 7.56       |
| Yiping Wang, 2018   | −0.88 (−1.34, −0.42) | 7.69       |
| Overall ($I^2$ = 93.8%, $p$ = 0.000) | −1.03 (−1.48, −0.59) | 100.00     |

Note: Weights are from random effects analysis
believed that long-term insulin insufficiency could lead to a more severe and extensive damage of T4 deiodination [55]. Type 2 deiodinase (Dio2) is an intracellular enzyme that catalyzes the conversion of T4 to T3 [62]. A meta-analysis showed that the polymorphism of Dio2 Thr92Ala is associated with poor blood glucose control in patients with T2DM [63].

The limitation of this study is that meta-analysis is a secondary literature analysis based on previous research evidence, so there are limitations and bias in the analysis. The study lacked data for long-term follow-up. The methods used to measure thyroid hormones were much less sensitive than those used in the last decade.
### Table 3
| Study ID       | SMD (95% CI)          | Weight (%) |
|----------------|-----------------------|------------|
| 1 Yan Zhao1    | -0.48 (-0.90, -0.07)  | 18.54      |
|                |                       |            |
| Shengbin Liu1  | -0.68 (-1.24, -0.13)  | 17.00      |
|                |                       |            |
| Subtotal (I-squared = 0.0%, p = 0.573) | -0.56 (-0.89, -0.22) | 35.54 |

### Table 4
| Study ID       | SMD (95% CI)          | Weight (%) |
|----------------|-----------------------|------------|
| 1 Yan Zhao1    | -1.86 (-2.30, -1.42)  | 18.25      |
|                |                       |            |
| Shengbin Liu1  | -1.72 (-2.53, -0.91)  | 14.08      |
|                |                       |            |
| Subtotal (I-squared = 0.0%, p = 0.764) | -1.83 (-2.22, -1.44) | 32.33 |

Note: Weights are from random effects analysis.
Figure 7: Comparison of severity of DKA and thyroid function in patients with diabetes and DKA.
5. Conclusion
Thyroid function changed in patients with DKA. It changed with the severity of DKA. This condition may be transient, preceding further recovery of DKA.

Data Availability
The data used to support the findings of this study are included within the article.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

References
[1] E. Karslioglu French, A. C. Donihi, and M. T. Korytkowski, "Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients," BMJ, vol. 365, p. 11114, 2019.
[2] D. Dabelea, A. Rewers, J. M. Stafford et al., “Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study,” Pediatrics, vol. 133, no. 4, pp. e938–e945, 2014.
[3] O. Pinhas-Hamiel, L. M. Dolan, and P. S. Zeitler, "Diabetic ketoacidosis among obese African-American adolescents with NIDDM," Diabetes Care, vol. 20, no. 4, pp. 484–486, 1997.
[4] C. R. Scott, J. M. Smith, M. M. Craddock, and C. Pithoker, "Characteristics of youth-onset noninsulin-dependent diabetes mellitus and insulin-dependent diabetes mellitus at diagnosis," Pediatrics, vol. 100, no. 1, pp. 84–91, 1997.
[5] A. K. Maniatis, S. H. Goehrig, D. Gao, A. Rewers, P. Walravens, and G. J. Klingensmith, "Increased incidence and severity of diabetic ketoacidosis among uninsured children with newly diagnosed type 1 diabetes mellitus," Pediatric Diabetes, vol. 6, no. 2, pp. 79–83, 2005.
[6] C. M. Alexander, E. M. Kaptein, S. M. C. Lum, C. A. Spencer, D. Kumar, and J. T. Nicoloff, "Pattern of recovery of thyroid hormone indices associated with treatment of diabetes mellitus," The Journal of Clinical Endocrinology & Metabolism, vol. 54, no. 2, pp. 362–366, 1982.
[7] A. P. Farwell, "Nonthyroidal illness syndrome," Current Opinion in Endocrinology & Diabetes and Obesity, vol. 20, no. 5, pp. 478–484, 2013.
[8] S. Rai, J. A. Kumar, K. P. Shetty et al., "Thyroid function in type 2 diabetes mellitus and in diabetic nephropathy," Journal of Clinical and Diagnostic Research: JCDR, vol. 7, no. 8, pp. 1583–1585, 2013.
[9] K. K. Dhatariya and G. E. Umpierrez, "Guidelines for management of diabetic ketoacidosis: time to revise?" The Lancet Diabetes & Endocrinology, vol. 5, no. 5, pp. 321–323, 2017.
[10] D. Chen, Y. Gao, and S. Xu, "Changes of thyroid hormones before and after treatment of diabetic ketoacidosis," Journal of Hainan Medical University, vol. 02, pp. 14-15, 1999.
[11] D. Ginoer, R. Naeije, J. Golstein, M. Fernandez-Deville, and L. Vanhaelst, "Alterations in circulating thyroid hormones and thyroxine-binding globulin levels during diabetic ketoacidosis," Journal of Endocrinological Investigation, vol. 3, no. 1, pp. 67–69, 1980.
mellitus," *Hormone and Metabolic Research*, vol. 21, no. 09, pp. 494–497, 1989.

[29] L. Luo, D. Deng, and C. Wang, "Changes of thyroid hormone levels in patients with diabetic ketoacidosis," *Anhui Medical and Pharmaceutical Journal*, vol. 09, pp. 1317–1318, 2012.

[30] J. L. Schilinger, A. Anceau, G. Chabrier, M. L. North, and F. Stephan, "Effect of diabetic control on the level of circulating thyroid hormones," *Diabetologia*, vol. 22, no. 6, pp. 486–488, 1982.

[31] Y. Zhao, B. Ynag, L. Huang et al., "201 cases of type 1 diabetes with low triiodothyronine syndrome," *Chinese Journal of Applied Clinical Pediatrics*, vol. 08, pp. 594–610, 2012.

[32] Y. Qiao, "Analysis of thyroid function in patients with diabetic ketoacidosis," Master thesis, Beijing University of Chinese Medicine, Beijing, China, 2012.

[33] S. Liu, "To explore the relationship between the changes of thyroid function and the condition in patients with diabetic ketoacidosis and hyperglycemia hypertonicity," Master thesis, Guangxi Medical University, Nanning, China, 2016.

[34] Q. Chen, M. Lu, Z. Ji et al., "Analysis of serum thyroid hormone levels in diabetic patients with ketoacidosis," *Preventive Medicine*, vol. 28, no. 03, pp. 268–269+273, 2016.

[35] B. Liu, "Study on the relationship between serum thyroid stimulating hormone and thyroid hormone levels in patients with type 2 diabetes," *Proceeding of Clinical Medicine*, vol. 04, pp. 284–286, 2012.

[36] J. Qiu, H. Qiu, H. Wang et al., "Effect of diabetic ketoacidosis on thyroid function," *Chinese Journal of Diabetes*, vol. 09, pp. 756–759, 2018.

[37] Y. Xin, M. Yang, X. J. Chen, Y. J. Tong, and L. H. Zhang, "Clinical features at the onset of childhood type 1 diabetes mellitus in Shenyang, China," *Journal of Paediatrics and Child Health*, vol. 46, no. 4, pp. 171–175, 2010.

[38] K. Derkach, I. Bogush, L. Berstein, and A. Shpakov, "The influence of intranasal insulin on hypothalamic-pituitary-thyroid Axis in normal and diabetic rats," *Hormone and Metabolic Research*, vol. 47, no. 12, pp. 916–924, 2015.

[39] L. Piconi, L. Quagliaro, R. Da Ros et al., "Intermittent high glucose enhances ICAM-1, VCAM-1, E-selectin and inter-leukin-6 expression in human umbilical endothelial cells in culture: the role of poly(ADP-ribose) polymerase," *Journal of Thrombosis and Haemostasis*, vol. 2, no. 8, pp. 1453–1459, 2004.

[40] S. M. Adler and L. Wartofsky, "Mechanisms behind the non-thyroidal illness syndrome," *Annals of Internal Medicine*, vol. 87, no. 6, pp. 760–768, 1977.

[41] C. S. Pittman, A. K. Suda, J. B. Chambers Jr., H. G. McDaniel, G. Y. Ray, and B. K. Preston, "Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy," *The Journal of Clinical Endocrinology & Metabolism*, vol. 48, no. 5, pp. 854–860, 1979.

[42] M. Inada, J. Okabe, Y. Kazama, H. Takayama, T. Nakagawa, and K. Torizuka, "Thyroid hormone turnover and transport in diabetes mellitus," *The Journal of Clinical Endocrinology & Metabolism*, vol. 36, no. 3, pp. 390–397, 1973.

[43] S. W. Spaulding, I. J. Chopra, R. S. Sherwin, and S. S. Lyall, "Effect of caloric restriction and dietary composition on serum T3and reverse T3in man," *The Journal of Clinical Endocrinology & Metabolism*, vol. 42, no. 1, pp. 197–200, 1976.

[44] G. Bray, D. Fisher, and I. Chopra, "Relation of thyroid hormones to body weight," *The Lancet*, vol. 307, no. 7971, pp. 1206–1208, 1976.

[45] A. R. C. Harris, S.-L. Fang, A. G. Vagenakis, and L. E. Braverman, "Effect of starvation, nutrient replacement, and hypothroidism on in vitro hepatic T4 to T3 conversion in the rat," *Metabolism*, vol. 27, no. 11, pp. 1690–1690, 1978.

[46] S. L. Welle and R. G. Campbell, "Decrease in resting metabolic rate during rapid weight loss is reversed by low dose thyroid hormone treatment," *Metabolism*, vol. 35, no. 4, pp. 289–291, 1986.
[61] C. S. Pittman, A. K. Suda, J. B. Chambers Jr., and G. Y. Ray, “Impaired 3,5,3′-triiodothyronine (T3) production in diabetic patients,” *Metabolism*, vol. 28, no. 4, pp. 333–338, 1979.

[62] A. C. Bianco, D. Salvatore, B. Gereben, M. J. Berry, and P. R. Larsen, “Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodi-
nases,” *Endocrine Reviews*, vol. 23, no. 1, pp. 38–89, 2002.

[63] X. Zhang, J. Sun, W. Han et al., “The type 2 deiodinase Thr92Ala polymorphism is associated with worse glycemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis,” *Journal of Diabetes Research*, vol. 2016, Article ID 5928726, 2016.