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MEDICINE

Haematological Indices and Anaemia in Patients with Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis

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Abstract

The objective of this paper is to systematically review and meta-analyse the relationship between haematological indices, anaemia and their significance in patients with type 2 diabetes mellitus (T2DM). A search of studies was conducted in the main databases (Medline, PubMed, EMBASE and Google Scholar) and the reference lists of selected studies. Comparative cross-sectional and case-control studies that met the eligibility criteria were included in this meta-analysis. There was no limitation in terms of language. Two independent researchers performed study selection and data extraction. Meta-analyses with random, fixed-effects model and subgroup analyses were performed. Publication bias was visualised by funnel plots. Quality of studies was evaluated following modified Downs and Black guideline. A total of 79 studies were retrieved, and 13 were included in the meta-analyses. The glucose metabolic profiles were higher in T2DM in relative to control (standardised mean difference (SMD) = 0.85, 95% CI (0.64; 1.06), $p < 0.00001$). However, there was reduction in haematological indices (SMD = − 0.52, 95% CI (− 0.78; − 0.25), $p = 0.0001$), both reticulocyte and erythropoietin, (SMD = − 1.33, 95% CI (− 2.23; − 0.44), $p = 0.003$), iron profiles (SMD = − 1.38 (− 2.08; − 0.67), $p = 0.00001$) and total-iron binding capacity (mean difference (MD) = − 44.88 (− 45.75, − 43.98), $p < 0.00001$) in T2DM patient relative to control. Meta-analysis results suggest that T2DM patients develop anaemia as a result of reduced erythropoietin, reticulocytes, haemoglobin, haematocrit, mean cell volume and iron profiles.

Keywords Anaemia · Megaloblastic anaemia · Type 2 diabetes mellitus · Haematological indices

Introduction

Diabetes mellitus is a group of chronic metabolic disease induced by uncontrolled high blood glucose level [1]. The main features of type 2 diabetes (T2DM) include hyperglycaemia, hyperlipidaemia, pancreatic β-cell dysfunction and low-grade chronic inflammation [2]. Hyperglycaemia, in this case, arises from insulin resistance or its deficiency [2, 3].

Anaemia, a haematological disorder common in T2DM patients, contributes to the development and exacerbation of microvascular (nephropathy, neuropathy and retinopathy) and macrovascular complications (coronary artery disease (CAD), peripheral arterial disease and stroke) [4]. In addition, inhibition of erythropoietin secretion from the kidney as a result of chronic urinary disease increases the risk of developing anaemia in T2DM and further development of cardiovascular disease (CVD) [3, 5–7].

Previous studies showed an association between iron deficiency anaemia and glycated haemoglobin levels in diabetic patients [8–15] while other studies showed no statistical

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differences between the glycated haemoglobin levels in T2DM patients and controls [16, 17].

With these contradicting results about the association of glycated haemoglobin, haematological indices and anaemia in type 2 diabetes mellitus, with other studies demonstrating negative while other shows positive relationship in T2DM. Thus, the factors that determine the association among these parameters in T2DM remain unclear. It was, thus, this contradiction that motivated the present study; hence, we systematically reviewed and meta-analysed the available studies assessing the relationship of haematological indices and anaemia and their significance in patients with type 2 diabetes mellitus.

Methodology

All protocols reported in this systematic review and meta-analysis were carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 guideline [18] (PRISMA file 1).

PRISMA 2009 Checklist.

Search Strategy

A literature search was conducted electronically on PubMed, MEDLINE, EMBASE and Google scholar databases for potentially relevant studies. As a result of the high rate of type 2 diabetes mellitus recently, two independent researchers (KM and MSM) searched for studies published in the past 5 years on 24 November 2019. The filters were restricted to human studies only with no restrictions on languages. The two researchers reached a conclusion by a discussion where there is disagreement in terms of the number of studies retrieved, with arbitration by the third reviewer MMM. The Medical Subject-Heading (MeSH) terms such as "anaemia", "megaloblastic anaemia" and "type 2 diabetes mellitus" were used to search for eligible included studies, corresponding synonyms including hyperglycaemia and insulin-resistant were identified through a screening process. Furthermore, we searched relevant studies from the list of references of included studies for additional eligible studies that were not detected through electronic search.

Section/topic	No.	Checklist item	Reported on page no.
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
	15		5

(continued)

Risk of bias across studies		Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6–7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6–7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8–9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9–10
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

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Study Selection

Initially, duplicates were removed using the reference manager software Mendeley Desktop version 1.19.4 (Elsevier, Amsterdam, Netherlands). Then, the remaining studies were screened by title and abstract for relevance. Following the initial screening, the potentially relevant full-text studies were critically evaluated for inclusion in the systematic review and meta-analysis. Study selection and screening process were done by two researchers (KM and MSM) independently. All disagreements in the study selection procedure were resolved through consensus by discussion among KM and MSM with arbitration performed by MMM.

Eligibility Criteria

Inclusion Criteria

This systematic review and meta-analysis included comparative cross-sectional and case-control studies reporting on the development of anaemia or haematological parameters in patients with type 2 diabetes mellitus in comparison to healthy controls.

Exclusion Criteria

Review papers, books, letters and editorials were excluded. Conference abstracts without full-text studies were also excluded. Additionally, studies that were conducted on T2DM without control were also were excluded.

Data Extraction

The important details of all eligible studies were independently extracted by two researchers (KM and MSM). These details were collected with a standardized data extraction sheet, including author and year of publication; country where the study was conducted; study design; population (number of participants in the T2DM compared to control groups); age, gender, body mass index (BMI); concentrations of haemoglobin (Hgb), glycated haemoglobin (HgbA1c), fasting blood glucose (FBG), mean corpuscular volume (MCV), total iron-binding capacity (TIBC), ferritin, erythropoietin, reticulocytes and haematocrit. We resolved disagreements through discussions with third author (MMM) until a consensus was reached. When multiple studies were published from the same dataset, to avoid duplication of data, we selected the study with the optimal sample size. In addition, the authors of other

studies with missing data were contacted through email. Mendeley reference manager version (1.19.4) software (Elsevier, Amsterdam, Netherlands) was used to save extracted data.

Quality Assessment and Risk of Bias

Two researchers (KM and MSM) independently assessed the quality and risk of bias of included study. KM evaluated the level of a disagreement using Cohen's kappa (http://justus.randolph.name/kappa) [19]. In case of disagreement, KM and MSM invited third reviewer MMM and reached a conclusion through a thorough discussion, re-evaluation of such studies for the quality. Moreover the same authors assessed the quality of included studies using modified Downs and Black guideline [20], the guideline consists of four domains which consider the reporting bias, external and internal validity, and lastly the selection bias (confounding).

Data Analysis

We used for Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) data analysis. We used the data (sample size, mean ± standard deviation (SD)) to explore the change of all outcome concentrations in T2DM compared to controls. Differences were expressed as standardised mean differences (SMDs) in case of differences in international system of units (SI) of outcome or mean difference in case of no difference in the SI of the outcome with the 95% confidence interval (CI). To calculate SMDs, mean values and their SD were employed. If the median and interquartile range (IQR) were reported, an online calculator was employed to estimate mean and SD [21]. Chi-squared and I^2 statistic tests were used in determining the level of heterogeneity across the included studies. The $I^2 = 0\%$, $I^2 \geq 50\%$ and $I^2 \geq 75\%$ were considered low, moderate and high level of heterogeneity, respectively. A random-effects model was employed where studies show a high level of heterogeneity or fixed-effects model where there is no heterogeneity between study characteristics. To find the possible source of heterogeneity, the test for subgroup analysis was performed. We assessed publication bias graphically through funnel plots. A p value of less than 0.05 was considered statistically significant.

Results

Selected Studies

A total of 79 studies were retrieved using the search strategy, and only 13 studies met the inclusion criteria, while studies 66 were excluded. Amongst the excluded studies, 10 were reviews and 56 were not relevant to the topic of interest and had different outcomes. Thirteen studies were included in the meta-analysis (Fig. 1).

The Characteristics of Included Studies

All included studies were published in peer-review journals from 2014 to 2019, and their characteristics are shown in Table 1. The included studies comprised of 6075 participants, 2137 (35.2%) of whom were T2DM, and 3938 (64.8%) were healthy controls. The sample size of included studies ranged between 28 and 2123 participants. Among the included 13 studies, ten were comparative cross-sectional and three were case-control studies. Briefly, six studies [8, 11, 13, 22–24] were published from 2014 to 2016 and seven studies [9, 10, 12, 17, 25–27] from 2017 and 2019. Three included studies were published in Korea, two studies in Senegal, 1 in China, 1 in Ghana, 1 in Romania, 1 in Spain, 1 in Nigeria, 1 in Brazil, 1 in Israel and 1 in Saudi Arabia (Table 1). There were differences in terms of the setting where the studies were conducted with most studies recruiting participants from either university hospitals, diabetic clinic hospitals or outpatient clinics.

Quality Assessment and Risk of Bias

The quality of included studies was assessed by using modified Downs and Black guideline as previously described. This checklist comprised of four domains which include (i) reporting bias, (ii) external validity, (iii) internal validity and (iv) selection bias (confounding). The evaluation was undertaken by two independent reviewers (KM and MSM) in order to eliminate the possibility of bias. KM applied appraised studies by both KM and MSM on an online Cohen's kappa calculator to assess disagreement. Briefly, where there was disagreement, the same reviewers invited the third reviewer (MMM) for adjudication and reached consensus through discussion and re-evaluation of the study in question. Overall, the included studies were of moderate quality with all studies scoring between the ranges of 13–18 out of the 26 items from the four domains of Downs and Black guideline (Table 1S).

Glucose Metabolic Profiles

The pooled effect estimate of glucose metabolic profile were higher in patients with T2DM in relative to control (SMD = 0.85, 95% CI (0.64; 1.06), $p < 0.00001$). In addition, these studies have shown a high level of statistical heterogeneity ($Chi^2 = 786.38$, $I^2 = 96\%$, $p < 0.00001$). As result of high heterogeneity, we further performed subgroup analysis and we found significant difference ($Chi^2 = 49.58$, $I^2 = 96\%$, $p < 0.00001$) between T2DM and control (Fig. 1S, Table 2S).

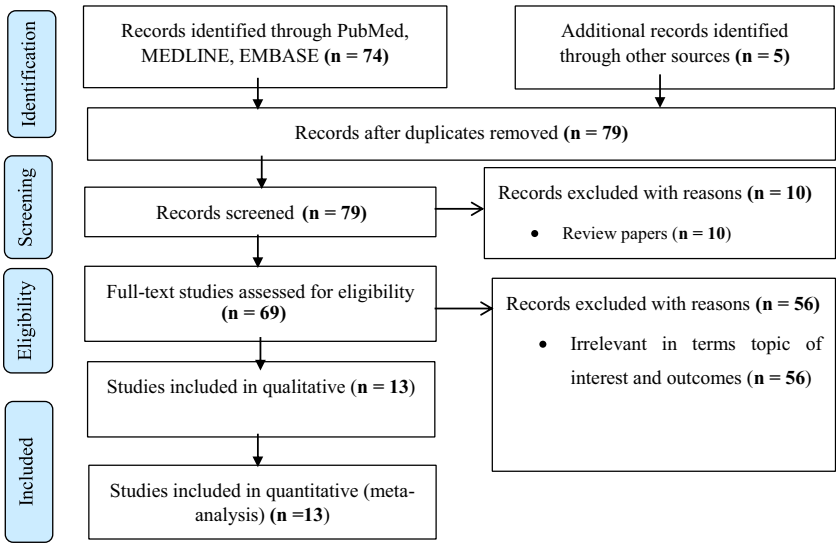

Fig. 1 PRISMA flow diagram of included studies

Haematological Profile

The pooled effect estimate of haematological indices were significantly reduced in T2DM patients in relative to control (SMD = − 0.52, 95% CI (− 0.78; − 0.25), $p = 0.0001$). As a result of high heterogeneity across the included studies ($Chi^2 = 446.49$, $I^2 = 96$, $p < 0.00001$), we carried out meta-analysis subgrouping and found that there was significant difference ($Chi^2 = 19.82$, $I^2 = 89.9$, $p < 0.0001$) amongst the groups (Fig. 2, Table 2S). We visually assessed publication bias by using funnel plots, and perfect symmetry was noted, which shows no presence of publication bias (Fig. 2S).

Erythropoiesis-Stimulating Agents like Erythropoietin in the Production of Erythrocytes

Both reticulocyte and erythropoietin pooled effect estimate were significantly reduced in T2DM patients relative to control (SMD = − 1.33, 95% CI (− 2.23; − 0.44), $p = 0.003$). However, the included studies had high nature of heterogeneity ($Chi^2 = 173.14$, $I^2 = 97$, $p < 0.00001$); as a result, we conducted subgroup analysis on both reticulocyte and stimulating growth factor (erythropoietin), and we observed no statistical significant difference among the groups ($Chi^2 = 1.7$, $I^2 = 41.2$, $p = 0.19$) (Fig. 3, Table 2S).

Iron Profile in Type 2 Diabetes Mellitus

Pooled effect estimate for iron profiles were significantly reduced in T2DM patients relative to control (SMD = − 1.38 (− 2.08; − 0.67), $p = 0.00001$). The level of heterogeneity among the included studies was significantly very high ($Chi^2 = 209.27$, $I^2 = 96$, $p < 0.00001$). Hence, we conducted subgroup analysis which showed statistically significant difference between the studies ($Chi^2 = 6.69$, $I^2 = 85.1$, $p = 0.0001$). However, iron (Fe) had non-significant moderate heterogeneity ($Chi^2 = 5.34$, $I^2 = 44$, $p = 0.15$) with significant overall effect (Fig. 4, Table 2S).

TIBC in Type 2 Diabetes Mellitus

Two studies reported total iron-binding capacity (TIBC); their meta-analysis overall effect has shown statistically significant reduction of TIBC in T2DM patient relative to control (MD = − 44.88 (− 45.75, − 43.98), $p < 0.00001$). Of interest, the above studies have showed no heterogeneity although this was not significant ($Chi^2 = 0.04$, $I^2 = 0$, $p = 0.83$) (Fig. 5, Table 2S).

Quality and Risk of Biasness

Three of the included studies showed a good score in terms of quality and bias with a rating range of 17–18 out of 26 items, whereas ten were rated as fair due to score of 14–15 (Table 1S).

Discussion

This study is the primary systematic review and meta-analysis evaluating the haematological profile, anaemia and their significance in T2DM patients. Critically evaluated data in this systematic review and meta-analysis revealed reduced haematological indices, iron profile (iron, ferritin, TIBC), immature red blood cell (reticulocytes), erythropoietin, elevated fasting blood glucose and glycated haemoglobin. However, we observed no statistically significant differences in terms of individual parameters including BMI, mean corpuscular volume, and haematocrit between patients with T2DM and the control.

Table 1 Characteristics of included studies

Author	Country	Study design	Participants (T2DM, control)	Age	Gender, M (%)	Main findings
Antwi-Bafour, 2016	Ghana	Case-control	100 (50, 50)	55.62 ± 10.37 44.11 ± 15.30	15 (44) 14 (39)	Significant increase in fasting blood glucose (FBG), and erythropoietin in T2DM with decrease in haemoglobin (Hgb) compared to control.
Aljohani, 2018	Saudi Arabia	Case-control	50 (25, 25)	54.89 ± 9.98 45.10 ± 14.77	8 (32) 7 (28)	There was a significant decrease in both haemoglobin and haematocrit (Hct)
Awofisoye, 2019	Nigeria	Cross-sectional	228 (150, 78)	50.00 ± 64.10 92.00 ± 59.40	45 (29.0) 17 (21.8)	Significant decrease in haemoglobin and increased glycated haemoglobin (HgbA1c) in T2DM.
Barbieri, 2015	Brazil	Cross-sectional	146 (50, 96)	61.80 ± 9.50 60.50 ± 8.70	23 (46.0) 29 (30.2)	Statistically significant decrease in both haemoglobin and haematocrit were observed in T2DM compared to control.
Broide, 2018	Israel	Case-control	28 (16, 12)	73.00 ± 20.74 68.00 ± 4.44	7 (44) 4 (33)	Significant decrease in haemoglobin in T2DM compared to control.
Chung, 2019	Korea	Cross-sectional	1637 (570, 1067)	61.50 ± 12.70 58.10 ± 13.30	268 (47) 529 (49.6)	Significant reduction in haemoglobin levels in T2DM compared to control.
Gradinaru, 2015	Romania	Cross-sectional	67 (37, 30)	70.00 ± 6.00 69.00 ± 5.00	16 (43) 18 (60)	Significant decrease in both haemoglobin and haematocrit, with increase in glycated Hgb and FBG
Hong, 2015	Korea	Cross-sectional	118 (55, 63)	54.10 ± 11.10 57.80 ± 8.70	25 (45.5) 32 (51)	Significant decrease in Hgb in T2DM anaemic patients compared to control
Lee, 2018	Korea	Cross-sectional	2123 (391, 1732)	60.10 ± 0.70 57.40 ± 0.40	54 (3.2) 55.3 (1.4)	The level of glycated Hgb significantly increased in T2DM when compared to control.
Mor Diaw, 2015	Senegal	Cross-sectional	28 (14, 14)	52.80 ± 11.60 40.40 ± 5.70	7 (50) 8 (57)	FBG and HgbA1c levels were higher in T2DM compared to control.
Skinner, 2018	Senegal	Cross-Sectional	108 (52, 56)	53.10 ± 8.40 50.00 ± 6.50	15 (29) 18 (32)	The concentration of glycated Hgb was higher in T2DM compared to control.
Traveset, 2016	Spain	Cross-sectional	312 (153, 159)	95 ± 5.83 95 ± 5.83	NR	Hgb and Hct showed no statistical difference between T2DM and control.
Wu, 2017	China	Cross-sectional	1134 (574, 560)	61.00 ± 8.70 53.20 ± 10.60	307 (53) 338 (60)	Significant decrease in Hgb was noted in T2DM compared to control.

Data expressed as mean± standard deviation, number (percentage), total (total per group)

NR not reported, *Hb1Ac* glycated haemoglobin, *Hgb* haemoglobin, *Hct* haematocrit, *FBG* fasting blood glucose

Diabetic patients frequently present with anaemia which is common blood disorders resulting into development and exacerbation of micro- and macrovascular complications [4]. It is regarded as an indicator of chronic urinary disease and increases the risk of developing cardiovascular disease (CVD) [3, 6]. In addition, systemic inflammation and inhibition of erythropoietin secretion from the kidney arising from chronic kidney disease increase the risk of developing anaemia in T2DM [28].

The body mass index (BMI) showed no difference between the patient with T2DM and control. BMI provides the most useful population-level measure of overweight and obesity, which is thought to be the primary cause of T2DM, although the patients with T2DM are known to have raised BMI, in this meta-analysis, it was not the case, as we found no significant difference among the groups. Increased BMI is associated with the risk of developing inflammatory disorders inclusive of obesity, T2DM and associated CVD [29]. Furthermore, as anticipated, FBG levels were significantly raised in T2DM relative to control. Raised FBG in patients with T2DM is a result of either deficiency of insulin or insulin resistance inducing hyperglycaemia [2, 30].

Glycated haemoglobin levels were also raised in T2DM. Glycated haemoglobin (HgbA1c) is a marker that predicts states of blood glucose over the previous 3 months. Other studies have shown that haemolytic anaemia, haemoglobinopathies, acute and chronic blood loss, pregnancy and uraemia result into reduction of glycated Hb as the lifespan of the red blood cell is shortened due to early destruction [31]. Red blood cell (RBC) lifespan in T2DM is decreased as a result of haematopoietic alteration arising from, chronic hyperglycaemia and hyperosmolarity [32, 33]. This alteration increases internal viscosity and membrane rigidity activation in these blood cells, thus reducing the number of red blood cells [34]. On the other hand, splenectomy and iron deficiency anaemia elevate the levels of glycated haemoglobin as this increases red cell lifespan [14, 16, 35, 36]. Hence, from this meta-analysis, we can suggest that the form of anaemia that the patients had was iron deficiency as it resulted in increased glycated haemoglobin in T2DM patients. Thus, it is concluded from the result generated from this meta-

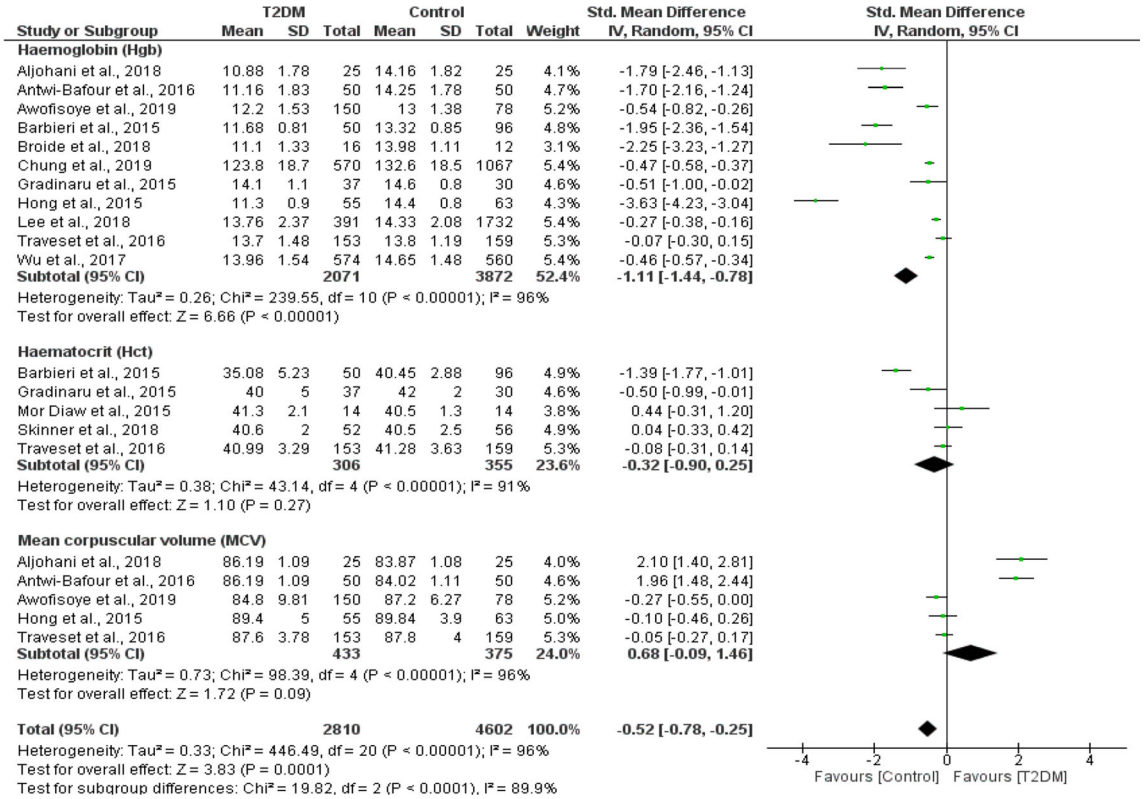

Fig. 2 Forest plot of comparison of haematological indices

analysis that T2DM is positively associated with glycated haemoglobin.

Our results have shown that reticulocytes, which are the immature form of red blood cells, were reduced in T2DM patients; although this was not significant, it is known that anaemic patients have reduced RBC counts which are likely to arise from low reticulocytes. Erythropoietin is a growth-stimulating factor or hormone required in development and maturation of normoblasts which are early forms of red cells; thus, its reduction signifies that the level and production of subsequent red blood cell will be diminished. Only one study showed an increase in erythropoietin; however, the level of reticulocyte was not determined, hence not enough information about the association of red blood cell and erythropoietin in such study. Based on haemopoietic process, erythropoietin has a direct relationship with the level of reticulocyte been produced [37]; thus, this was supported by the results obtained from this study. Thus, we can conclude that reduced production of erythropoietin leads to decreased production of red blood cells lineages.

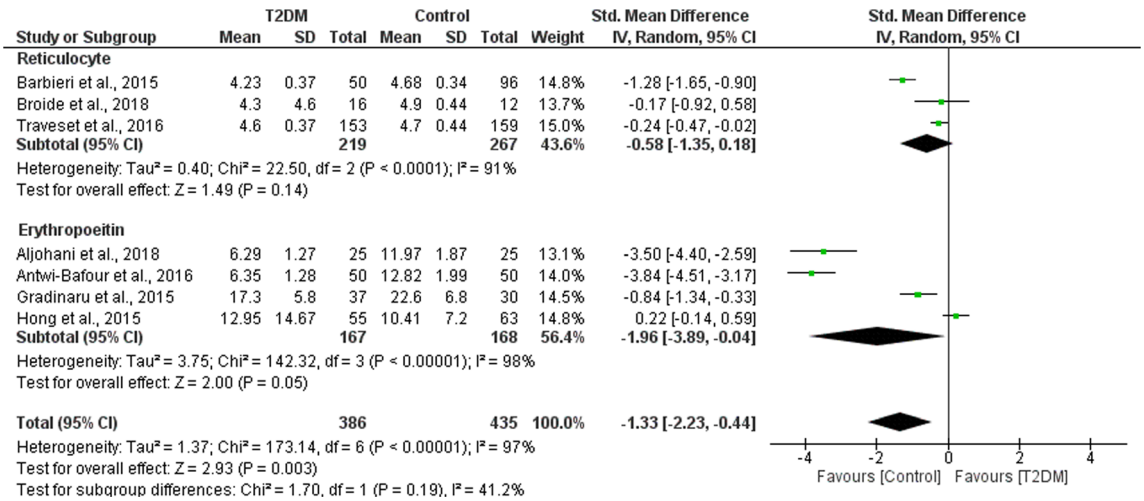

Fig. 3 Forest plot of comparison of reticulocyte and erythropoietin

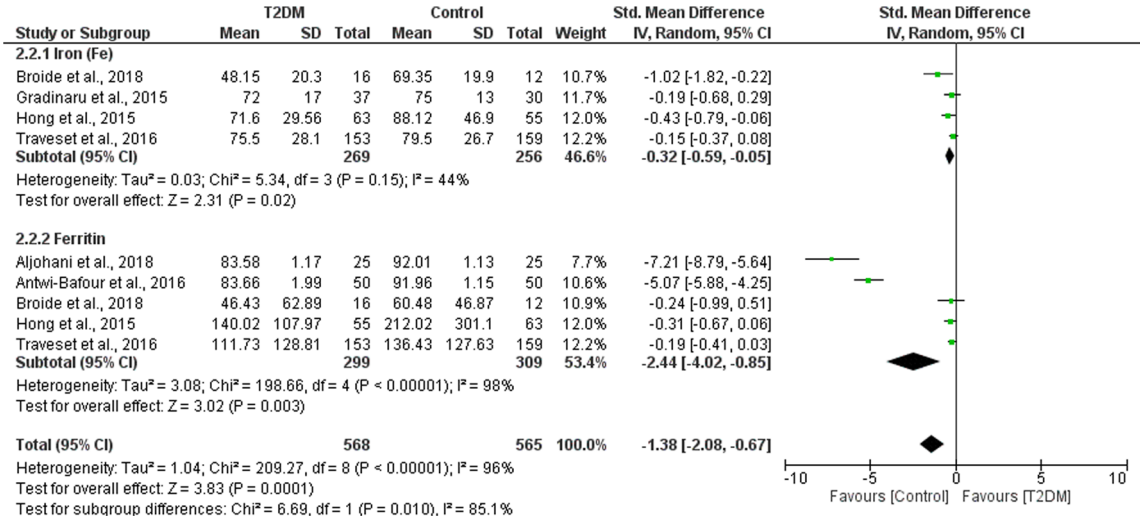

Fig. 4 Forest plot of comparison of iron profile in T2DM and control

Iron deficiency anaemic patients present with low haemoglobin (Hgb), haematocrit (Hct) and low mean corpuscular volume (MCV) [38] while megaloblastic anaemia is characterized by macrocytes (high MCV) [39]; this is supported by findings from this meta-analysis; however, other studies have shown contradictory findings as they had high percentage of haematocrit and levels of MCV [8, 10]. This can be explained partly by the form of anaemia the patient might have had at the time of the investigations. The presented high MCV, coupled with low haemoglobin in T2DM, suggests that the patient had macrocytic anaemia.

The levels of ferritin were significantly decreased in T2DM relative to control. Ferritin is known as a regulator of iron metabolism and used in the evaluation of iron status. However, its level does not necessarily demonstrate total body iron storage in some case, as it reflects inflammatory conditions, insulin resistance, and T2DM [40]. Additionally, elevated iron stores below the levels of haematochromatosis (iron overload) depict the progression of T2DM [40, 41]. This is supported by the findings generated in this meta-analysis.

TIBC reflects the ability of iron to bind to the substrate of interest; in this study, we have shown that T2DM patients have reduced iron-binding capacity. Thus, it is presumed that high iron in T2DM patient may have impaired or dysfunctional binding sites.

Conclusion

From this systematic review and meta-analysis, we found that type 2 diabetes mellitus patients develop anaemia as a result of reduced erythropoietin, immature red blood cells (reticulocytes), haemoglobin, haematocrit and MCV which are major red blood cell indices, which further predisposes patients with T2DM to secondary complications such as nephropathy. Thus, therapeutic technique that can control anaemia in T2DM may be of relevance in regulating or prevention of secondary complications associated with T2DM.

Limitations

High heterogeneity due to variations in study design as other studies was cross-sectional and case-control in nature; secondly, origin where studies were conducted also played a role in the level of heterogeneity. However, the random-effect model was employed to account for heterogeneity. Additionally, variations in population size with other studies having larger and some having smaller sample size. Type 2 diabetes mellitus is a chronic condition; hence, the duration of its occurrence is of the essence; however, most of the included studies did not report this parameter, and thus, it was not considered for inclusion when extracting data. Lastly, the inability to determine

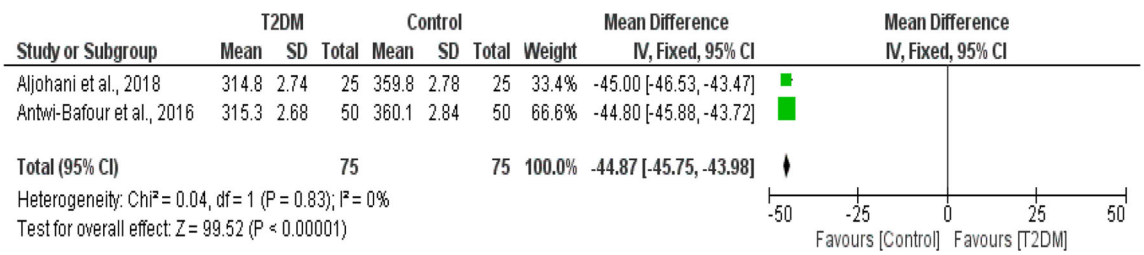

Fig. 5 Forest plot of TIBC in T2DM and control

the form of anaemia in each included study also could have affected the results.

Recommendation

Future clinical studies should determine the types of anaemia in order to give accurate or precise suggestion and recommendations.

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Author Contribution KM, MSM and MMM contributed equally from conceptualisation, screening, statistical analysis, writing first draft, editing and final approval for publication of this manuscript.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Ethical Considerations Not required as this is review and analyse studies that are already published.

Abbreviation BMI, Body mass index; EPO, Erythropoietin; FBG, Fasting blood glucose; Fe, Iron; Hct, Haematocrit; Hgb, Haemoglobin; MCV, Mean corpuscular volume; Retics, Reticulocytes; TIBC, Total iron-binding capacity; T2DM, type 2 diabetes mellitus; HgbA1c, glycated haemoglobin

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