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The role of interleukin-1 β in type 2 diabetes mellitus: A systematic review and meta-analysis

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Type 2 diabetes mellitus (T2DM) is a multifactorial non-communicable disease that is characterized by insulin resistance and chronic sub-clinical inflammation. Among the emerging inflammatory markers observed to be associated with β -cell damage is interleukin 1 β (IL1 β), a proinflammatory cytokine that modulates important metabolic processes including insulin secretion and β -cell apoptosis. The present systematic review and meta-analysis gathers available evidence on the emerging role of IL1 β in T2DM. PubMed and Embase were searched for human studies that assessed IL1 β in T2DM individuals from 2016-2021. Thirteen studies (N=2680; T2DM=1182, controls=1498) out of 523 were included in the systematic review and only 3 studies in the meta-analysis. Assays were the most commonly used quantification method and lipopolysaccharides as the most common stimulator for IL1 β upregulation. Random and fixed effects meta-analysis showed non-significant mean differences of IL1 β concentrations between the T2DM and controls. Given the high heterogeneity and small subset of studies included, caution is advised in the interpretation of results. The present systematic review and meta-analysis highlights the limited evidence available that could implicate IL1 β as a potent biomarker for T2DM. Standardization of IL1 β assays with larger sample sizes are encouraged in future observational and prospective studies.

KEYWORDS

type 2 diabetes mellitus, interleukin 1 β , inflammasome, inflammation, inflammatory disease, cytokines

Introduction

According to the International Diabetes Federation (IDF), 451 (CI 367.5–585.5) million people aged 18–99 years lived with diabetes as of 2017 (1). This figure is predicted to rise to 693 (CI 521.9–902.5) million by 2045, or 281% higher from data taken in 2000 (1). Type 2 diabetes mellitus (T2DM) reduces life expectancy by as much as one decade (2). A particular feature of T2DM is chronic hyperglycemia caused by genetic and environmental factors with concomitant defects in both β -cells' insulin action and secretion (in fat, muscle, liver and elsewhere) (3). T2DM is considered a chronic inflammatory disease with high circulating levels of tumor necrosis factor (TNF), interleukins and adipokines (4).

Important sensors of T2DM metabolic dysfunction and β -cell dysregulation are known as inflammasomes. Inflammasomes are cytosolic macromolecular complexes that contain a sensing element that can activate an inflammatory response to an array of signals (5). The most extensively investigated inflammasome complex is the NLRP3 inflammasome (5). It is made up of the sensing protein (NLRP3), the adaptor protein; apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the effector protein; pro-caspase-1, forming an intracellular multi-protein complex that activates the synthesis of Interleukin-1 β (IL-1 β) and Interleukin-18 (IL-18) (6). It also represents an important link between the immune system and the metabolic system (7).

In general, it may be theorized that inflammasomes have an important role in the activation of chronic inflammation as observed in pro-inflammatory related diseases. Thus, the association of inflammasomes in the progress of pro-inflammatory related diseases is reasonable (4). Particularly, over expression of NLRP3 inflammasome is now identified as a key player in the development of numerous inflammatory and autoimmune diseases which include atherosclerosis, neurodegenerative diseases, obesity and T2DM (8–11). T2DM is caused partly by a state of low-grade inflammation due to excess nutrients and excess metabolic stress (metaflammation). Evidence also indicates a direct key function of the innate system in the destruction of β -cells (12) and impaired insulin secretion (13). Accumulating evidence points out that the inflammation status of T2DM islets has two key characteristics: elevated cytokine levels and increased activation of immune cells, mostly macrophages (14).

IL-1 β , a pro-inflammatory cytokine, has been underlined as a strong driver of β -cell damage. β -cell macrophages are the main contributors to IL-1 β production. IL-1 β levels, being a potent pro-inflammatory driving cytokine, is kept under strict regulation by IL-1 receptor antagonist (IL-1Ra). During inflammation, macrophages are the main source of IL-1 β /IL-1Ra, making both cytokines in an autoregulatory feed-back loop (Figure 1) (15). In comparison to other cells, β cells express an abundant number of interleukin 1 receptor (IL-1R). Thus, the balance in IL-1 β /IL-1Ra levels is crucial in defining the response

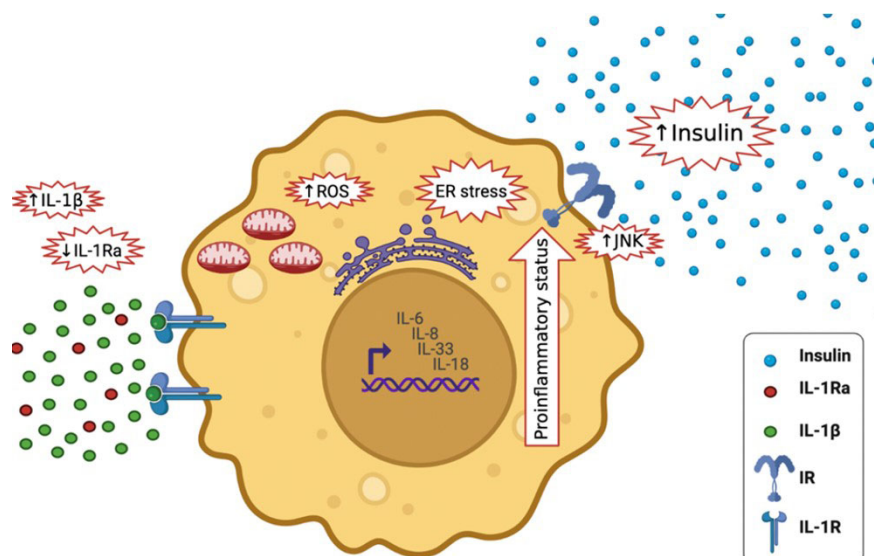


FIGURE 1

IL-1 β Synthesis and Regulation. NLRP3 inflammasome is activated via two signals; the priming signal which activates the transcription factor NF- κ B leading to the upregulation of NLRP3, pro-IL-1 β and IL-1Ra mRNA and the activation signal which stimulates NLRP3 inflammasome complex assembly and activation, assembled caspase-1 undergoes self-cleavage and activation. Active caspase-1 triggers the activation and release of IL-1 β . IL-1 β regulates its own synthesis in an autoregulatory feed-back loop (15).

of β -cells and ultimately the progression of T2DM (15). IL-1 β encompasses various functions in regulating inflammatory responses and metabolism; it can regulate insulin secretion and promote β cell apoptosis which can eventually lead to T2DM (4, 16). Chronically elevated IL-1 β levels in obese and T2DM individuals cause β -cell dysfunction (16). IL-1 β signaling events induce an acute phase response, low blood pressure, dilation of the blood vessels, and fever, which can ultimately result in large inflammatory events (17). Still, the role of inflammation, immune cells and interleukins in particular, in the pathogenesis of T2DM, remains a gray area in the field that requires further evaluation (18).

In the current systematic review and meta-analysis, we aimed to determine whether there is an association between T2DM and circulating IL-1 β based on available evidence from 2016-2021.

Methods

The current systematic review followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines (19). Figures 1 and 6 were created using BioRender software (BioRender, Toronto, ON, Canada).

Literature search

A systematic search in PubMed and Embase was done last 5 September 2021 using the keywords [Interleukin-1 beta AND type 2 diabetes mellitus].

Study selection

The inclusion criteria were as follows:

1. Case-control, observational studies and clinical trials conducted in human subjects that assessed IL-1 β in participants.
2. Studies written in the English language.
3. Studies with available free full text source.
4. Studies with adult participants (19+ years old).
5. Studies conducted in the last 5 years (2016-2021).

The exclusion criteria were as follows

1. Review articles.
2. Studies among nonhuman subjects.
3. Pre-existing disease in participants other than T2DM.
4. Studies that didn't measure IL-1 β in participants.
5. Sample type: stem cells, saliva, human umbilical cord MSCs, purified human islets co-cultured, animal and rat cell line
6. Sites that couldn't be accessed.

7. Studies that did not discriminate or exclude patients based on medical and medication history.

8. Studies that did not include T2DM patients.

Data extraction

Titles and abstracts of all articles were screened for eligibility. Full articles were retrieved for eligible abstracts if available and evaluated. For the evaluation of studies, CASP tool was used to evaluate the quality of all included studies (Supplementary 1). For the meta-analysis, review manager 5.4 <https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download> was used. Only case control studies were included. Two independent investigators (HA and SS) extracted pertinent data from eligible studies using a standard MS Excel spreadsheet with the senior investigator (NA) supervising entry. Information extracted included the full citation of the article, country where the investigation was done, study design, sample size, age, body mass index (BMI), number of males and females if available, methods used to assess IL-1 β and outcome.

Results

The systematic search strategy returned 523 articles. After applying the selection criteria, 13 articles were included (Figure 2). These studies included a total of 2680 adults, 1182 were T2DM cases (mean age 54.2 ± 6.7 years) and 1498 were controls (mean age 50.2 ± 6.2 years). Sample sizes ranged from 22 (20) to 1643 individuals (21). Mean BMI in the T2DM group (N=10 studies) was $26.9 \pm 3.2\text{kg/m}^2$, while the mean BMI in controls (N=8 studies) was $24.3 \pm 1.3\text{kg/m}^2$.

A total of 13 eligible studies (10 case control studies, 1 Prospective Randomized Controlled study, 1 interventional study and 1 prospective controlled study) were included in this systematic review and meta-analysis. Four studies were conducted in Europe, six in Asia and three in South America (Table 1). The mean and standard deviation of the T2DM group and the HC group was only mentioned in three studies.

Meta-analysis

A random effect model was applied for the mean difference of change between two groups. Meta-analysis was performed for outcomes examined in at least two studies, with provided mean values and standard deviation for each group. I-square test was used to measure heterogeneity between studies, and a value > 30.0 was considered to reflect high heterogeneity. Figures 3 and Figure 4 represent forest plots showing individual and pooled

TABLE 1 Summary of included studies.

Study Setting	Population (M/F)	Samples/Kit Used	Outcome	Strengths and Limitations
1 (15) Armenia	T2DM: N= 35 (15/20) Age= 53.8 (46-69) BMI= 25.7 ± 3.5 HC: N= 31(16/15) Age= 51.9 (40-67) BMI= 23.5 ± 2.6	Plasma samples and supernatants of cultured PBMCs/ELISA MAX Deluxe kit (Biolegend, USA)	* IL-1 β plasma levels are increased in T2DM patients (P = 0.038). * LPS stimulation increased release of IL-1 β compared to unstimulated samples except female patients. LPS induced IL-1 β production by PBMCs from HC and T2DM males (P = 0.01 and P = 0.03, respectively) and in HC females (P < 0.001).	* Hypomethylation of IL1RN and NFKB1 promotor regions in PBMCs of T2DM group and not in HC group.
2 (22) Armenia	T2DM: N= 17 (7/10) Age= 45.4 ± 10.1 BMI= 27.3 ± 2.4 HC: N= 15 Age= NM BMI= NM	Neutrophils Protein: ELISA MAX Deluxe kits (Biolegend, UK) mRNA: Hs01555410_m1 (AppliedBiosystems, Foster City CA, USA)	* Freshly isolated neutrophils from T2DM group did not exhibit significant differences in mRNA expression of IL-1 β gene as compared to HC group. * sFasL significantly increased mRNA levels of IL-1 β in neutrophils from T2DM group. * Protein levels of IL-1 β were not affected by the sFasL treatment (P>0.05).	* sFasL exhibited proinflammatory effect and induced mRNA levels of caspase-1, NF- κ B and IL-1 β . * Did not assess the impact of different therapy (gliclazide/metformin) on activation status of neutrophils. * HC group were not perfectly age-matched with the T2DM group. * Small sample size.
3 (16) Vietnam	T2DM: N= 73(40/33) Age= 55.7 ± 11.5 BMI= NM HC: N= 57 (12/45) Age= 48.5 ± 6.8 BMI= NM	Serum/AviBion Human IL-1 β (Orgenium, Helsinki, Finland)	* IL-1 β levels were significantly increased in T2DM group compared with the HC group. (P < 0.0001). * IL-1 β levels were not significantly different between the overweight and non-overweight T2DM group. * Adiponectin levels were negatively correlated with IL-1 β levels.	* Levels of adiponectin and IL-1 β are significantly modulated during the development of overweight and T2DM * Adiponectin levels are correlated with several pro-inflammatory cytokines including IL-1 β and with clinical parameters of obesity and T2DM. * Did not mention if age and sex were matched in the T2DM and the HC group.
4 (23) China	T2DM: N= 70 (45/25) Age= 51.31 ± 9.25 BMI= 24.84 ± 2.74 HC: N= 32 (13/19) Age= 52.41 ± 8.57 BMI= 23.71 ± 2.60	Blood/enzyme immunoassay kits (R&D systems, Minneapolis, MN)	* No significant difference in IL-1 β protein levels between the T2DM and the HC group. * No significant difference in IL-1 β levels between the acarbose-treated and metformin-treated T2DM subgroups. * No significant differences in IL-1 β levels were observed between the T2DM patients and the HC after 12 months of treatment. * After 6 months or 12 months of treatment, the variation margins of IL-2, IL-6, IL-1 β , TNF- α and ferritin levels were similar between the acarbose-treated and metformin-treated T2DM subgroups.	* Chronic inflammatory status is not improved as quickly as glucose metabolism and required a long-lasting therapy (>12month). * Small sample size. * No placebo/control group. * Did not determine whether the effect of a longer term (>12month) treatment on the levels of inflammatory factors reduced vascular complications.
5 (24) India	T2DM: N= 80 Age= NM BMI=NM HC: N= 80 Age= NM BMI= NM	Serum/Cytometric Bead Array (CBA) method 558279 (IL-1 β flex set)	* IL-1 β levels were significantly increased in the T2DM group (P= 0.019) in early middle aged (31-40 years) and not effected in late middle aged (41-50 years) (P=0.167). * IL-1 β did not show a significant association with ageing among the T2DM group.	* Oxidative stress and proinflammatory markers (including IL-1 β) were significantly increased in the early-middle-aged (31-40 years) T2DM group compared to the HC group. * One-point single-centered study.
6 (21) India	T2DM: N= 558 (293/265) Age= 57.29 ± 9.41	Whole blood/quantitative PCR using SYBR Green method and their respective forward and reverse primers (Eurofins, Bangalore, India) Real-time PCR (LightCycler480 Real-	* No difference in the genotype and allele frequencies (IL-1 β -511C/T polymorphism) was observed between the T2DM and the HC group. * There was also no difference between	* The study proposes the possible involvement of IL-1 β polymorphisms for genetic susceptibility to T2DM in Gujarat population. * Limited to Gujarat population.

(Continued)

TABLE 1 Continued

Study Setting	Population (M/F)	Samples/Kit Used	Outcome	Strengths and Limitations
7 (25)	T2DM: N= 141(60/81) Age= 56.5 ± 10.7 BMI= 23.5 ± 3.5 HC: N= 22 (11/11) Age= 51.6 ± 6.0 BMI= 23.0 ± 2.6	Time PCR, Roche) was performed in duplicate in 10 µl volume using LightCycler480 SYBR Green I Master mix (Roche Diagnostics GmbH, Mannheim, Germany) as per the instruction manual Plasma/DLB50, R&D systems	genotype frequency TT vs TC while TT vs CC frequency differed significantly in the T2DM and the HC group. * mRNA levels of IL-1β were significantly higher in the T2DM group compared to the HC group. * 4-fold higher expression of IL-1β transcript in the T2DM group compared to the HC group. * IL-1β levels were significantly increased in patients with T2DM (P <0.001). * The circulating cell-free mitochondrial DNA (ccf-mtDNA) levels were increased in patients with type 2 diabetes. * Weak correlation between the elevated ccf-mtDNA levels and IL-1β levels in plasma from patients with type 2 diabetes.	* Provides evidence that elevated ccf-mtDNA levels may contribute to chronic inflammation in patients with type 2 diabetes. * Small sample size of HC group.
8 (26)	T2DM: N= 56(28/28) Age= 50.95 ± 12.48 BMI= 25.60 ± 3.69 IGT: N= 35 (17/18) Age= 51.85 ± 8.57 BMI= 23.88 ± 3.20 HC: N= 45 (22/23) Age= 52.29 ± 12.16 BMI= 23.16 ± 1.98	Serum/Human ELISA kit; USCN, Wuhan, China	* IL-1β levels were significantly increased in the IGT and T2DM groups compared to the HC group (P <0.001). * IL-1β levels were significantly increased in the T2DM group compared to the IGT group (P <0.001). * Serum adipsin levels was negatively correlated with IL-1β levels.	* This is the first study to investigate the relationship between serum adipsin levels and the first phase of insulin secretion in humans with different glucose tolerance. * Small sample size.
9 (27)	T2DM: N= 38 Age= 61.2 ± 6.8 BMI= NM HC: N= 31 Age= 61.9 ± 11.3 BMI= NM	Blood monocyte/ELISA BioSource, Nivelles, Belgium	* No significant differences in the concentration of IL-1β released by monocytes cultured in (low, normal, and high glucose concentrations, with and without LPS stimulation) between the T2DM and the HC group. * Low glucose concentration increased IL-1β production by monocytes from the T2DM and HC group pre and post LPS stimulation. * IL-1β production was unaffected by high glucose concentrations in both the T2DM and the HC group.	* First study to provide evidence that low glucose concentrations may be a powerful stimulus for proinflammatory cytokine expression (IL-1β) by human monocytes. * Small sample size.
10 (28)	T2DM: N= 31 (31/0) Age= 48 (45,58) BMI= 33.3 (27.5, 46.7) HC: N= (27/0)	Venous blood, PBMC mRNA: Real-time quantitative PCR technology Protein: Immun-Star™ Western CTM Chemi-luminescence Kit (cat# 170-5070; Bio-Rad	* I-1β mRNA and protein levels were significantly increased in the T2DM group compared to the HC group. * This induction was notably suppressed after 24 h treatment with recombinant β 1-, β 3- and β 6-conglutin proteins.	* 1, β3, and β6 proteins can regulate the level of mRNA and protein synthesis of crucial genes involved in the insulin molecular signaling pathway, thereby modulating the activation and response of these regulatory genes leading to variation in insulin-mediated plasma glucose levels.

(Continued)

TABLE 1 Continued

Study Setting	Population (M/F)	Samples/Kit Used	Outcome	Strengths and Limitations
11 (20) Brazil	Age= 50 (40,53) BMI= 24.8 (23, 26.6) T2DM: N= 10 (0/10) Age= 70 ± 3 BMI= 28.4 ± 1.4 HC: N= 12 (0/12) Age= 62.9 ± 1.8 BMI= 26.6 ± 1.2	Plasma and neutrophils/DuoSet ELISA kits (R&D Systems, Minneapolis, MN, USA)	* Four months of dance training did not modify plasma IL-1 β levels in the T2DM and the HC group. * Before training there was no difference for neutrophil IL-1 β production in the T2DM and the HC group. * After training there was no difference in neutrophil IL-1 β production between the T2DM and the HC group following LPS stimulation.	* Small sample size. * All participants were male. * This research was the first to investigate neutrophil function and death after a moderate-intensity dance program in people with T2DM. * These findings may represent a useful tool to design nonpharmacological strategies to reduce inflammation and improve neutrophil clearance in patients with T2DM. * Small sample size. * All participants were female.
12 (29) Mexico	T2DM: N= 43 (15/28) Age= 53 [30- 68] BMI= 26 [23- 47] HC: N= 26 (9/17) Age= 48 [33- 65] BMI= 26 [23- 33]	Whole blood monocytes/ Cytometric bead array (BD Bioscience)	* No significant difference in IL-1 β production in response to Pam3Cys, LPS and <i>M. tuberculosis</i> infection between the T2DM and the HC group. * Decreased IL-1 β production in monocytes cultured in high glucose for 24 h and after stimulation with LPS.	* Provides evidence that the presence of high glucose concentrations decreased cytokine production and increased the intracellular growth of <i>M. tuberculosis</i> in monocytes. * Small sample size. * No mention if age and sex were matched in the T2DM and the HC group.
13 (30) Argentina	T2DM: N= 30(23/7) Age= 48.17 (23–69) BMI= 33.17 (30.82–38.64)	Serum and mononuclear leucocyte mRNA levels/ chemiluminescence (Immolute – Siemens, DPC) Quantitative real time PCR with the StepOne system (Applied Biosystems)	* At baseline, serum IL-1 β levels positively correlated with FPG. * Significant association between T allele (CT and TT) and lower IL-1 β mRNA expression. * IL-1 β mRNA and protein levels had no differences with pre-intervention time. * Sharper decreases in FPG and HbA1c after treatment were associated with greater reductions in IL-1 β protein levels.	* First follow-up study evaluating IL-1 β mRNA expression and serum levels in a hyperglycemic T2DM group and after glycemic normalization treatment. * Short post-intervention study time. * This study was carried out in a population with different proportions of men and women.

T2DM, Type 2 Diabetes Mellitus; N, Number; BMI, Body Mass Index; PBMC, Peripheral Blood Mononuclear Cell; ELISA, Enzyme Linked Immunosorbent Assay; IL-1 β , Interleukin 1 Beta; LPS, Lipopolysaccharides; IL1RN, Interleukin 1 Receptor Antagonist Gene; NFkB1, Nuclear Factor Kappa B Subunit 1 Gene; mRNA, Messenger RNA; sFasL, Soluble Fas Ligand; HC, Healthy Control; PCR, Polymerase Chain Reaction; SYBR, Synergy Brands; ccf-mtDNA, Circulating Cell Free Mitochondrial DNA; IGT, Impaired Glucose Tolerance; NGT, Normal Glucose Tolerance; NM, Not Mentioned; Pam3Cys, Palmitoylated N-acyl-S-diacylglycerol Cysteine; *M. Tuberculosis* Mycobacterium Tuberculosis; FPG, Fasting Plasma Glucose.

mean differences (95% CI) of IL1 β concentration in T2DM and control subjects. The forest plots provided non-significant mean differences of IL1 β concentration between the T2DM and controls with the pooled mean difference of 2476.7 (-4057.56 – 9010.96) and -320.58 (-1133.29 – 492.13) after removing the study of Bae and colleagues (2019) due to extremely high heterogeneity, as shown in Figures 3 and Figure 4 respectively. Both I^2 statistics which were well above the threshold of 50% indicate heterogeneity among the included studies.

IL-1 β protein

IL-1 β protein levels were assessed in 12 studies, with no uniformity in assays used for assessment (Table 1). Two studies observed significantly higher IL-1 β protein levels in the T2DM group than controls (15, 25). Protein levels of IL-1 β were

unaffected by the sFasL treatment in both T2DM and control groups (22). In the study of Tong and colleagues (2017), IL-1 β protein levels didn't differ between the overweight and non-overweight T2DM groups. However, in the control groups, IL-1 β levels were higher in the overweight group than the non-overweight group (16). In one trial, 6 months of acarbose or metformin treatment, IL-1 β protein levels were substantially lower in the T2DM group (23). With regards to age, Banerjee et al. (24) recorded significantly higher IL-1 β protein levels in the younger (31-40 years) T2DM group versus age-matched controls and no difference in G2 (41-50 years) T2DM group versus G2 controls. Zhou et al. (26) recorded elevated IL-1 β protein levels in both the impaired glucose tolerance (IGT) and T2DM groups than controls. Piarulli et al. (27) recorded elevated IL-1 β protein levels in monocytes cultured with low-glucose

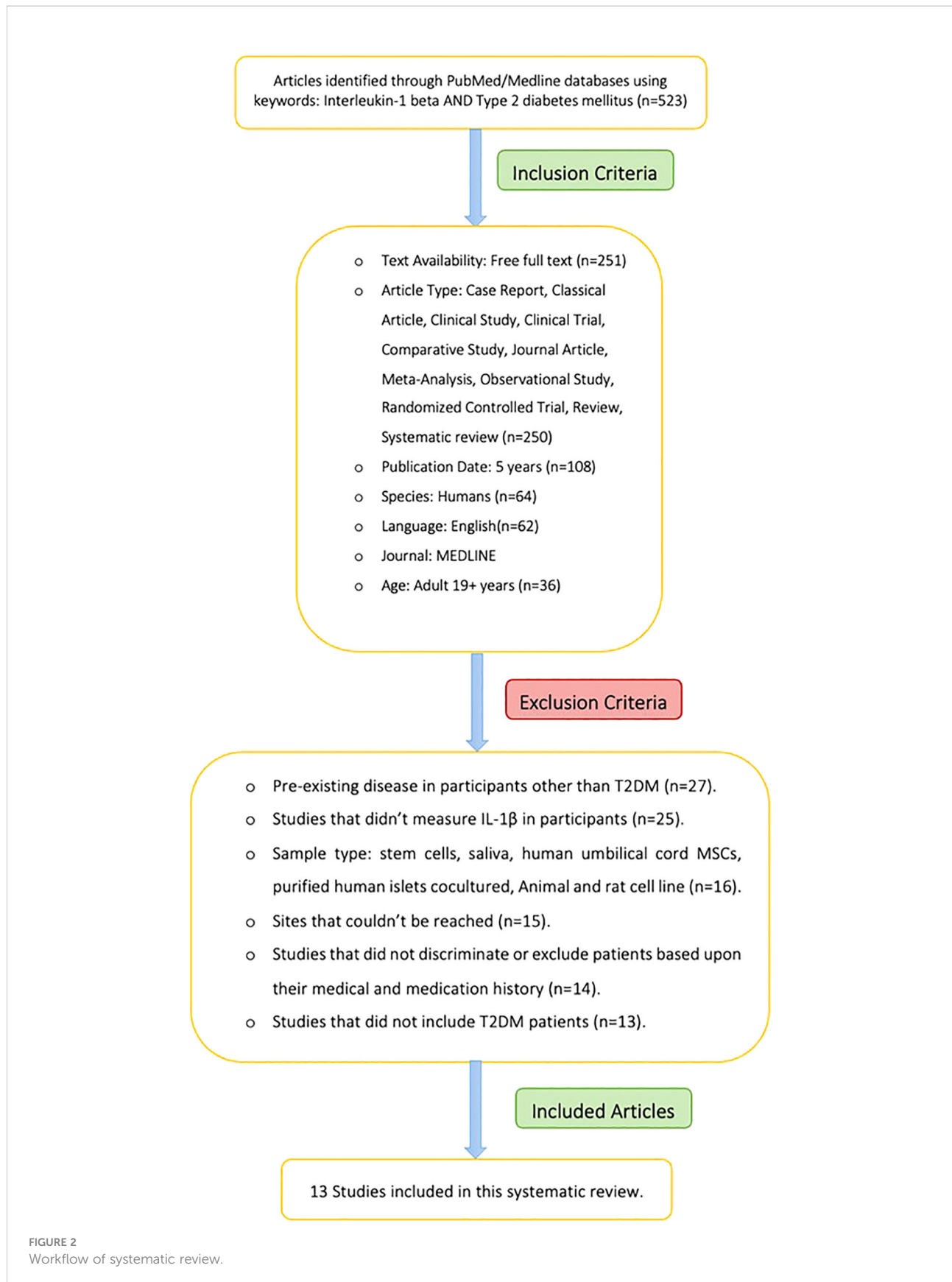


FIGURE 2
Workflow of systematic review.

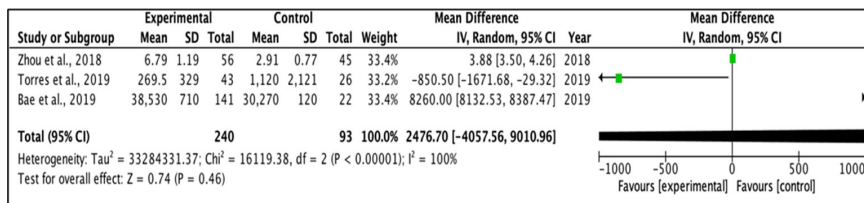


FIGURE 3 Forest plot for analysis of IL-1β levels.

levels with and without LPS stimulation, which was not the same for normal/high glucose culture. Lima-Cabello et al. (28) recorded elevated IL-1β protein levels in the T2DM group which decreased after day 1 of incubation with β1, β3, and β6 purified β-conglutin proteins. Borges et al. (20) observed no substantial difference in neutrophil IL-1β levels in the T2DM group and controls pre/post-dance training intervention. Torres et al. (29) also observed no substantial difference in monocyte IL-1β protein levels in T2DM and controls post Pam3Cys or LPS, or M. tuberculosis infection activation. Circulating IL-1β decreased after high-glucose culture for day 1 and post activation with Pam3Cys or LPS or M. tuberculosis infection for 1 day. Iglesias Molli et al. (30) no substantial difference in IL-1β protein levels pre/post pharmacological treatment and changes in regimen was observed. However, the higher reduction in fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) after treatment were associated with sharper reduction in IL-1β protein levels.

IL-1β mRNA

IL-1β mRNA levels were assessed in 4 studies. Two studies did not observe a substantial difference in mRNA levels between T2DM and controls. (21) observed that IL-1β mRNA levels were 4 times higher in the T2DM group than controls. sFasL stimulation significantly increased mRNA levels of IL-1β in neutrophils in the T2DM group. Elevated IL-1β mRNA levels were notably suppressed after day 1 of incubation with β1, β3, and β6 purified β-conglutin proteins (28).

Intervention

In the study of Margaryan et al. (15), participants were receiving nutritional therapy recommendations and T2DM patients were receiving gliclazide and metformin. Furthermore, in an earlier investigation of Margaryan et al. (22), all T2DM participants were on diet therapy and oral hypoglycemic agents (N=5 gliclazide and N=12 metformin). In Tong et al. (16), participants newly diagnosed T2DM participants were either on gliclazide MR and/or a low dose of insulin injection. In Mo et al. (23), participants received four weeks of lifestyle therapy based on the Chinese diabetes management guidelines, with T2DM participants randomly assigned (1:1) to receive metformin or acarbose treatment. In Banerjee et al., (2020), most participants were on metformin in combination with other class of hypoglycemic drugs. In Zhou et al. (26), all the participants were placed on a diet consisting of 150 g of carbohydrate/day for 3 days before the test. In Piarulli et al. (27), 10 T2DM patients were on statins, 26 on antihypertensive drugs, and 9 on aspirin 100 mg/day. In Borges et al. (20), participants received dance training classes that consisted of 60 min of exercise carried out twice a week for 4 months. Four participants from the control group were on lipid-lowering agents, 1 was taking ACE inhibitor, 3 on beta-blocker I, 1 was taking diuretics and 3 were taking angiotensin II. In the T2DM group, 6 were on insulin, 6 were on metformin, 1 on lipid-lowering agents, 2 on ACE inhibitors, 3 on beta-blocker I, 1 on diuretics and 3 on angiotensin II. In Iglesias Molli et al. (30),

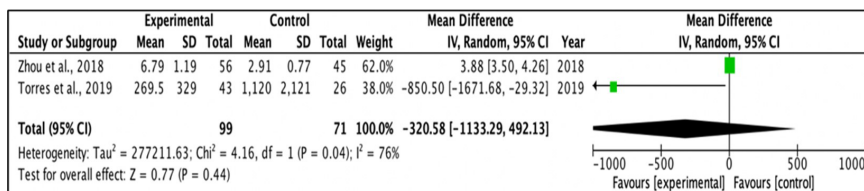


FIGURE 4 Forest plot for analysis of IL-1β levels.

participants underwent changes in lifestyle to achieve the target metabolic control (HbA1c under 7%). Each participant received personalized pharmacological treatment. The pharmacological treatment of choice in 19 participants was metformin in doses between 500 and 2550 mg/day; 5 participants received combined treatment with metformin and insulin; 1 participant received metformin and glibenclamide; 1 participant received vildagliptin; and 1 participant did not receive pharmacological treatment.

Genetic analysis

Three studies undertook genetic analysis. Margaryan et al. (15) questioned whether DNA methylation status of *IL1RN*, *RELA* (*p65*) and *NFKB1* (*p50*) genes may be relevant to IL-1 β and IL-1Ra production and may be a possible contributory factor in the inflammatory pathogenesis of T2DM (1). Patel et al. (21) performed genotyping of neuropeptide Y (NPY) and IL-1 β single nucleotide polymorphisms (SNPs). The allele and genotype frequencies for *IL1B* -511C/T polymorphism were calculated in T2DM and controls. Iglesias Molli et al. (30) evaluated the association between the rs16944 genotype with mRNA expression, serum levels of IL-1 β , biochemical and clinical variables.

Indicators of glucose tolerance and insulin sensitivity

Glucose tolerance and insulin sensitivity were assessed in most studies by different methods. Ten studies measured FPG (15, 16, 21, 22, 24, 26–30), one study (30) only had T2DM group. Eleven studies measured HbA1c (15, 16, 22–30). Four studies (16, 22, 25, 30) only measured HbA1c in the T2DM group. Banerjee et al. (24) measured fasting plasma insulin and Zhou et al. (26) measured fasting serum insulin. Three studies (16, 24, 26) assessed homeostatic model assessment for insulin resistance (HOMA-IR), Tong et al. (16) calculated homeostatic model assessment of β -cell function (HOMA- β) and quantitative insulin-sensitivity check index (QUICKI). Zhou et al. (26) calculated acute insulin response (AIR) and first-phase insulin secretion (AUC) while (23) conducted a standard meal test (500 kilocalories of energy intake).

Baseline characteristics

Twelve studies reported the age of participants included (15, 16, 20, 21, 23–30). Margaryan et al. (22) only mentioned the age of the T2DM group and not the HC group and Iglesias Molli et al. (30) only had T2DM participants. Five studies reported a significant difference in the age between the T2DM and healthy

controls (HC) (16, 20, 24, 25, 28). Banerjee et al. (24) reported a significant difference in the G1 subgroup (age 31–40 years). Three studies did not report a significant difference in the age between the T2DM group and HC (23, 26, 27) and Banerjee et al. (24) did not report a significant difference in the G2 subgroup (age 41–50 years). Four studies did not mention the difference in age between the T2DM group and the HC group. (15, 21, 22, 29)

Twelve studies reported the sex of the participants (15, 16, 20, 21, 23–30). Margaryan et al. (22) only mentioned the sex of the T2DM group and not the HC group and Iglesias Molli et al. (30) only had T2DM participants. Only two studies (16, 23) reported a significant difference in the sex distribution between the T2DM group and the HC group. Four studies did not mention the difference in sex between the T2DM and the HC group (15, 21, 22, 27). In two studies (20, 24) participants were all females while Lima-Cabello et al. (28) participants were all males.

Eleven studies reported BMI (15, 16, 20, 21, 23–26, 28–30). Margaryan et al. (22) only mentioned the BMI of the T2DM group and Iglesias Molli et al. (30) only had T2DM participants. Four studies (21, 23, 26, 28) reported a significant difference in the BMI between the T2DM and the HC group; Banerjee et al. (24) reported a significant difference in the G1 subgroup (age 31–40 years). Four studies (16, 20, 25, 29) did not report a significant difference in the BMI between the T2DM and the HC group. Three studies (15, 22, 27) did not mention the difference in BMI between the T2DM and the HC groups.

Baseline lipid profile

Nine studies reported HDL levels (15, 16, 20, 21, 23, 24, 26, 29, 30), Margaryan et al. (22) only mentioned HDL levels in the T2DM group. Two studies (21, 29) reported a significant difference in the HDL levels between groups, while four studies (20, 23, 26, 29) did not report a significant difference in the HDL levels between the T2DM and the HC groups. Two studies (15, 22) did not mention the difference in HDL levels between the T2DM and the HC group.

Nine studies reported the LDL levels (15, 16, 20, 21, 23, 24, 26, 29, 30). Three studies reported a significant difference in the LDL levels between the T2DM and the HC group (16, 21, 23). Four studies did not report a significant difference in LDL levels between the T2DM and the HC group (20, 24, 26, 29).

Nine studies reported triglyceride (TG) and total cholesterol (TC) levels (16, 20, 21, 23–26, 29, 30). Seven studies reported a significant difference in the TG levels between the T2DM and the HC group (16, 21, 23–26, 29). (20) did not report a significant difference in the TG levels between the T2DM group and the HC group. Two studies (16, 23) reported a significant difference in the TC levels between groups. Six studies did not report a significant difference in the TC levels between the T2DM and the HC group (20, 21, 24–26, 29).

Discussion

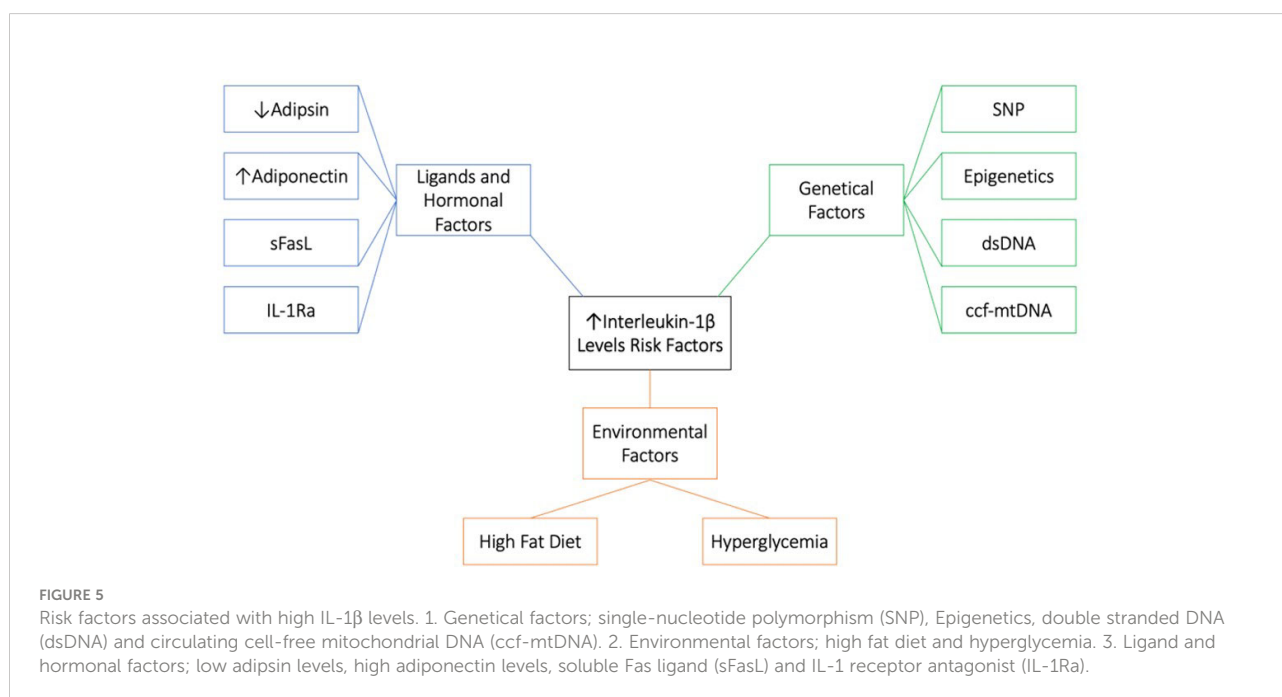
The current systematic review and meta-analysis covers for the first time a small number of studies assessing IL-1 β levels in a T2DM group and in a HC group. Only 13 studies met the pre-defined inclusion criteria, and one of these studies only measured IL-1 β in the T2DM group (30). According to these limited studies, IL-1 β levels were mostly elevated in the T2DM group and directly proportional with FPG and HbA1c levels. Meta-analysis indicates high heterogeneity between the studies this could be due to the large age scale included in the meta-analysis, differences in the duration of the disease between the patients or differences in the study assay or design. IL-1 β levels were also affected by age, BMI and many genetical, hormonal and environmental factors (Figure 5). Treatment with either or both metformin and acarbose had a nullifying result on IL-1 β levels in the T2DM group.

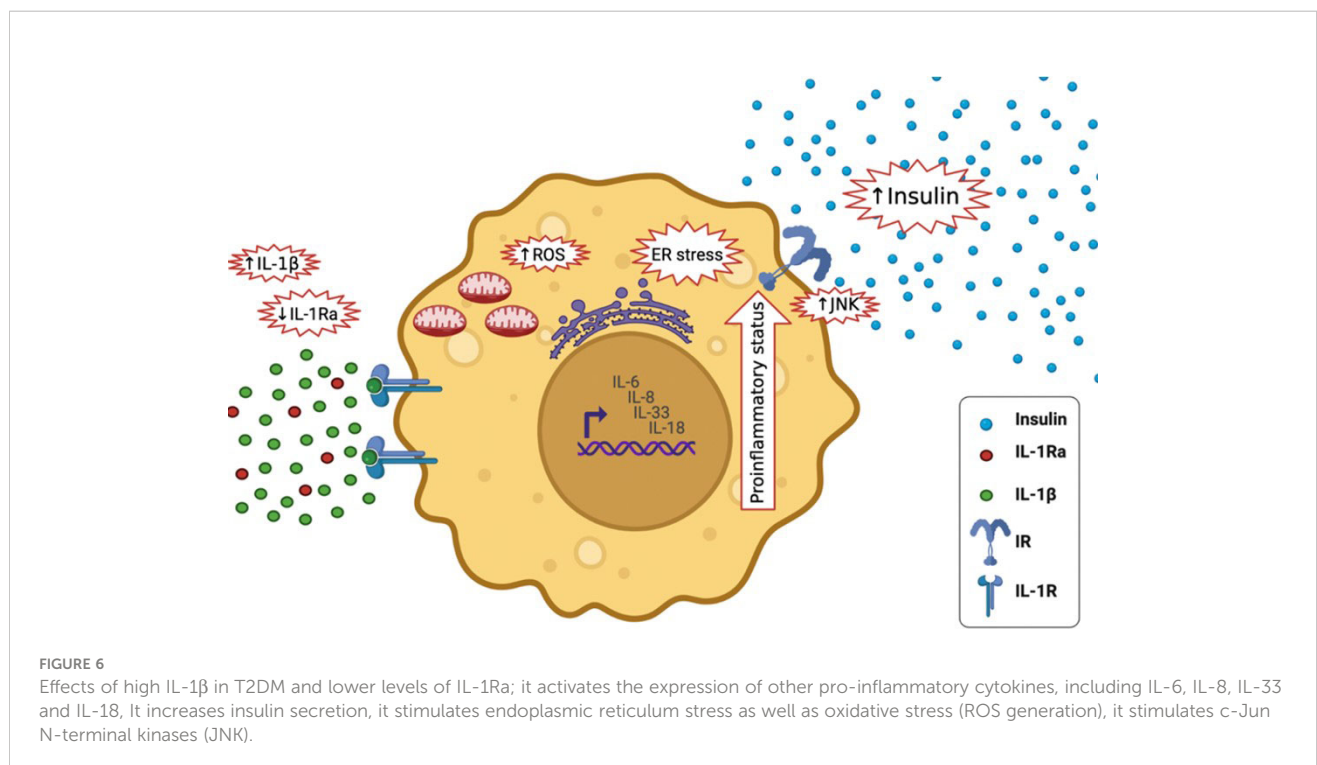
How can the physiological role of IL-1 β switch to a pathological role in β cell failure and apoptosis? There are a couple of explanations for the double-edged sword effect of IL-1 β ; 1) Lower-levels of IL-1 β prevents β -cell apoptosis and stimulates β -cell propagation and glucose activated insulin production. Whereas higher-levels of IL-1 β exhaust β cells and have contrary consequences. Thus, IL-1 β might play a part in both β -cell apoptosis and propagation (31, 32). IL-1 β signaling in β cells is also more prolonged and aperiodic. While momentary exposure to macrophage derived IL-1 β can increase insulin levels, prolonged exposure to IL-1 β can cause β cell compensation. The signaling shift from the physiological protein kinase C (PKC) and diacylglycerol (DAG) pathways to

the pathological mitogen-activated protein kinase (MAPK) and nuclear factor kappa light chain enhancer of activated β cells (NF- κ B) pathways might influence the concentration and time dependent effects of IL-1 β exposure (33). 2) Long-lasting activation of β cells by IL-1 β may lead to resistance or unresponsiveness. Opposing to β -cells from healthy subjects, those from T2DM patients lack insulin secretion following stimulation by miniscule levels of IL-1 β (31). 3) There may be inadequate IL-1Ra in β cells (Figure 6). IL-1Ra is a protecting protein stimulated by IL-1 β itself to trigger a negative feedback loop (31). 4) Long-lasting activation of β cells by IL-1 β may ultimately change the transcriptional program, disturbing the cell's identity, proliferation, and death (31).

Elevated IL-1 β levels in T2DM activates the expression of other inflammatory cytokines, including IL-6, IL-8 (33), IL-33 and IL-18, and amplifying the pro-inflammatory environment (34). It increases insulin secretion temporary, which maybe maleficent to metabolism (35). Furthermore, it stimulates endoplasmic reticulum and oxidative stress, both of which are tightly associated to T2DM (36). It also stimulates c-Jun N-terminal kinases (JNK), activating serine-phosphorylation of insulin receptor substrate-1 (IRS-1) and reducing the activity of insulin-PI3K/PKB signaling pathway in insulin responsive cells (37) (Figure 6). During glucose activation, β -cells release IL-1 β , IL-1 β in a positive feed-back vicious cycle activates its own synthesis in β cells and attracts macrophages act as an additional source of IL-1 β and other cytokines (32). Prolonged innate immune stimulation activates diabetes and linked diseases (33).

Obesity is linked to low-grade systemic inflammation that progresses to metabolic diseases as well as insulin resistance





accompanied by altered resident immune cells in adipose tissue (38). Obese patients have an upregulation in NLRP3 and IL-1 β expression in intra-abdominal and sub-cutaneous fat and this was confirmed by genetic analysis (39–41), eventually leading to NLRP3 inflammasome activation and caspase-1-mediated IL-1 β and IL-18 secretion and pyroptosis (38). Pyroptosis is an inflammatory type of programmed cell death that is crucial for IL-1 β release because it lacks a signal sequence for exocytosis (42).

Consumption of saturated fatty acids (SFA) is tightly related to obesity and has been correlated with IR and inflammatory diseases in humans. SFA suppresses AMP-activated protein kinase (AMPK) which increases mtROS production and hinders autophagy, leading the activation of the NLRP3 inflammasome and IL-1 β driven IR (38). Managing weight and calory intake can contradict this upregulation. Hence, implying that obesity induced insulin resistance (IR) and NLRP3 inflammasome activation are interconnected (39–41). Vandanmagsar et al. outlined an important function of the NLRP3 inflammasome in this inflammatory obesity induced disease where danger associated molecular patterns (DAMP), such as oxidized LDL and cholesterol crystals induce a NLRP3 and IL-1 β driven pro-inflammatory reaction (43). Lipopolysaccharides (LPS) are one of the most vigorous pathogen associated molecular patterns “PAMP” for priming the NLRP3 inflammasome, they upregulate the expression of NLRP3 and pro-IL-1 β . Blood levels

of LPS rise because of increased gut permeability and changes in gut microbiota in T2DM patients who are obese (44).

The authors acknowledge some limitations which should be taken into consideration in the interpretation of the review presented. Only 13 studies met the inclusion criteria and some of these were limited by small sample sizes, one without a HC group, one with all male subjects and one with all female subjects and one study was limited to a certain population. Furthermore, expanding the search up to 2010 led to no additional eligible studies. The mean and standard deviation of the T2DM group and the HC group was only mentioned in three studies. Other pertinent information such as duration of diabetes and physical activity were missing in the majority of studies, which, aside from the different assays used and the characteristics of the population, could have greatly contributed in the high heterogeneity of the analysis.

Conclusion

In conclusion, the limited studies included in the current systematic review and meta-analysis indicate high but non-significant IL-1 β levels in T2DM patients. Variations in assays, sample sizes, population characteristics and design make it difficult to harmonize available data. More studies, both observational and longitudinal, using standardized assays, are

necessary to conclude if IL-1 β can be a promising biomarker for T2DM.

Data availability statement

The original contributions presented in the study are included in the article/[supplementary material](#). Further inquiries can be directed to the corresponding author.

Author contributions

HA, SS and NA-D contributed in study conception and design; HA wrote the manuscript; SS, reviewed the manuscript; SS and NA-D supervised the review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2022.901616/full#supplementary-material>

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