SYSTEMATIC REVIEW

Surfactant protein-D, diabetes mellitus, oxidative stress, infections and inflammation on the crossroad: A Systematic review

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Abstract

Objective: To review the association of surfactant protein-D with type 2 diabetes mellitus, infections, oxidative stress and inflammation, and the changes in oxidative stress markers in type 2 diabetes mellitus.

Method: The systematic review was conducted from April to September 2022, and comprised search on PubMed, Web of Sciences, Scopus, Science Direct and Google Scholar databases for relevant studies published in English language between January 1, 2000, and June 30, 2022. The search was updated in September 2022. After transferring literature to Mendeley, relevant data was extracted from the included studies. Quality assessment for eligible studies was done using Joanna Briggs Institute Critical Appraisal Checklist. Quality of evidences was assessed by using Grading of Recommendations Assessment, Development and Evaluation tool.

Results: Of the 203 studies identified, 18(8.9%) were analysed; 16(89%) with humans and 2(11%) with animals as subjects There were 5 (31.25%) studies for SP-D, of which 4 (80%) studies reported lower surfactant protein-D in type 2 diabetes mellitus cases than controls. Its significant negative association with glycated haemoglobin was reported by 1(20%) study and 2(40%) studies with fasting blood glucose levels. Higher surfactant protein-D in type 2 diabetes mellitus cases and its positive association with glycated haemoglobin was reported by 1(20%) study. Recurrent infections were frequent in type 2 diabetes mellitus patients. Malondialdehyde level was higher and superoxide dismutase activity was lower in type 2 diabetes mellitus cases, reflecting oxidative stress. Animal studies also showed that reactive oxygen species generating from hypochlorous acid during oxidative stress promoted the formation of non-disulfide linkages in surfactant protein-D structure, resulting in its decreased functionality.

Conclusion: Surfactant protein-D, oxidative stress, inflammation and infections were found to be linked to each other for pathogenesis of infections in type 2 diabetes mellitus.

Keywords: Surfactant protein-D, Diabetes mellitus type 2, Oxidative stress, Infections, Superoxide dismutase, Malondialdehyde. (JPMA 74: 534; 2024) **DOI: https://doi.org/10.47391/JPMA.9977**

Introduction

Surfactant protein-D (SP-D) is a crucial component of immunity.[1] It plays distinct roles in the regulation of innate and adaptive immunity exerting antimicrobial effect for combating infections.[2,3] It is primarily produced in alveolar type II cells and non-ciliated Clara cells, but is also expressed in blood, heart, skin, gastrointestinal and urogenital tracts.[4] Its presence in extra-pulmonary tissues may be attributed to its leaking from alveolar capillaries into systematic circulation.[3] It is composed of a 43kD peptide chain with dodecameric cruciform structure having 4 trimetric subunits linked by disulphide bonds.[5,6] Each subunit has amino (NH_2)-terminal cross-linking domain, a collagenous, short-neck sequence, and a carboxyl(COOH) terminal, Calcium dependent (C-type) lectin domain called the carbohydrate recognition domain (CRD).[5,6] Disulfide linkage in amino terminal domain is crucial for stabilising its unique conserved structure required for host defense.[7] CRD is the active part that binds to immune cell receptors, as well as acts as a pattern-recognition receptor (PRR) that recognises and binds to pathogenic associated molecular pattern (PAMP) of pathogens.[7,8] It enhances clearance of microorganisms through opsonisation, agglutination, neutralisation and phagocytosis by macrophages and neutrophils that produce oxidative burst to facilitate killing and elimination of these pathogens.[6,9] It also prevents adherence and colonisation of microorganism in the airways by directly binding to them.[10] Oligosaccharides covering of microbes is an important determinant of self/non-self-antigen recognition.[11] CRD domain interacts preferentially with oligosaccharides of the microbes, but it has an affinity for binding with peptidoglycan and lipoteichoic acid (LTA) of gram-positive bacteria and lipopolysaccharides of gram-negative bacteria for initiating immune responses.[10,12] Recent studies demonstrated its distinctive role in modulating infection and inflammation caused by

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emerging viruses like Ebola virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human coronavirus 229E (HCoV-229E) strains of coronavirus, through neutralisation by interacting with their high mannose oligosaccharides covering.[13,14] SP-D is also inter-linked innate with adaptive immunity by modulating functions of T and dendritic cells.[15] Moreover, SP-D facilitates Neutrophil extracellular traps(NET)-mediated microbial trapping and killing of microorganisms during neutrophil-mediated host defense.[3] SP-D deficiency is associated with raised cytokine levels, inflammation, decreased phagocytosis and increased colonisation of pathogens, which emphasizes its vital role in immunity.[9,10]

SP-D functions as a double-edged sword causing damping of inflammation in casual environmental stimuli to avoid unnecessary tissue damage, whereas it promotes inflammatory responses when tissues are overwhelmed with injurious stimuli.[16,17] In the absence of infection, SP-D helps to maintain non-inflammatory environment in tissues via activating signal inhibitory regulatory protein alpha (SIRPα) pathway by phosphorylation of SIRPα.[17] SIRPα is a transmembrane inhibitory protein on alveolar macrophages, maintains quiet non-inflamed state in tissues by inactivating macrophages, and further promotes anti-inflammatory effect by increasing phosphorylation and activation of tyrosine phosphatase-1, which, in turn, causes downstream blockage of P38 mitogen-activated protein (MAP) kinase and Src family kinases (SFKs) signalling by decreasing their phosphorylation, leading to declined production of proinflammatory mediators.[16,17]

During the infection, binding CRD of SP-D to PAMPs on foreign organisms along with its simultaneous interaction with calreticulin/CD91 on the macrophages via its collagenous tails can initiate ingestion of foreign organisms by these immune cells. Previous studies have also demonstrated that interaction of SP-D with calreticulin/CD91 complex could initiate extensive proinflammatory and pro-immunogenic responses through activation of the P38 MAP kinase, nuclear transcription factors-kappa β (NF-kβ) and activator protein-1 (AP-1) signalling pathways.[13,17]

Type 2 diabetes mellitus (T2DM) is associated with recurrent infections involving all the systems, leading to psychological and physiological stress.[18] Pulmonary, cardiac, gastrointestinal, renal infections, cellulitis, rhinocerebral mucormycosis, limb and joint infections with serious consequences are common in T2DM.[19-21] Oxidative stress and inflammation are considered major pathways for immune dysregulation and development of recurrent infection in T2DM.[20,22] Deficiencies in numerous proteins, including SP-D, proved to be associated with dysregulation of glucose metabolism. Significant lower level of SP-D in T2DM has been evident in previous studies that run in parallel with inflammation and infections.[3,22] SP-D can augment immune responses against all pathogens to which patients with T2DM are susceptible, including bacteria, like *staphylococcus (S.) aureus, escherichia (E.) coli, klebsiella (K.) pneumonia, pseudomonas (P.) aeruginosa*, viruses like human immunodeficiency virus (HIV), influenza A virus, and fungi, including *Candida (C.) albicans, chlamydia (C.) trachomatis* and *cryptococcus neoformans* etc.[23] Possible reason for its lower level in diabetes is hyperglycaemia that can interfere with CRD and microorganism interaction. Protease inhibitor alpha 2 (α2) macroglobulin binds with the CRD domain of SP-D and defends it from elastase mediated degradation. High concentration of glucose can compete with α2 macroglobulin and also enhances elastase activity. Elastase will in turn cause cleavage and inactivation of CRD and weakening of SP-D functions in subjects with T2DM.[3] Furthermore, many researchers have suggested that oxidative modifications in its structure during oxidative stress adversely effects its function and host defense.[24,25] Numerous studies have attempted to correlate SP-D, infections, oxidative stress and T2DM, but still nothing has been established.[26,27]

Repeated inflammation in T2DM causes potential release of pro-inflammatory mediators, including tumour necrosis factor-alpha (TNFα) and gut-derived lipopolysaccharide (LPS), that further enhance insulin resistance (IR) in these patients.[28] TNFα and LPS activate NF-kB and Jun N-terminal kinase (JNK) intracellular signalling pathways, which, in turn, trigger up-regulation of genes that encode production of more inflammatory mediators, such as interleukin-6 (IL-6) and IL-1β that results in increased IR and oxidative stress generating ROS, hence, creating a vicious cycle.[28] Vicious cycle of inflammation-ROS-inflammation that develops in the bone marrow causes functional impairment of microglial and T cells that infiltrate into the tissue and further augment secretion of pro-inflammatory molecules that support the vicious cycle, leading to more lipid peroxidation triggering apoptotic pathway and cell death.[29,30]

Previous studies have demonstrated that hyperglycaemia in T2DM can trigger free radical production by hyperactivation of various biochemical pathways, like non-enzyme glycation of protein, glucose auto-oxidation, advanced glycation end-product (AGE), hexosamine pathway, polyol pathway flux, and activation of protein kinase C isoforms that result in over production of hydrogen peroxide (H_2O_2), superoxide and hydroxyl radicals accompanied by the amplified expression of

nicotinamide phosphate adenine dinucleotide (NADPH) oxidase. These results in more lipid peroxidation of poly unsaturated fatty acid, and excess release of byproduct of oxidant, malondialdehyde (MDA).[31-35]

Moreover, increased glycosylation of anti-oxidant enzyme superoxide dismutase (SOD) causes reduction in its activity and limitation of its capacity to detoxify oxygen radicals, leading to oxidative stress.[34,36] SOD is the first line of defence against oxidative tissue damage, and helps in the elimination of H_2O_2 from superoxide that can be later on decomposed into water and oxygen by catalase enzyme, and, hence, protects tissues from oxidative damage.[37,38] As such, imbalance between oxidant and antioxidant system in T2DM promotes oxidative stress in T2DM.[37]

The current systematic review was planned to investigate the emerging association of SP-D with T2DM, infection, inflammation and oxidative stress, and to explore changes on MDA level and SOD activity that reflect oxidative stress in T2DM.

Materials and Methods

The systematic review was conducted from April to September 2022, and comprised search on PubMed, Web of Sciences, Scopus, Science Direct and Google Scholar databases for relevant studies published between January 1, 2000, and June 30, 2022. The search was updated in September 2022. The systematic review was done in line with following the protocols of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) following the population-intervention-comparison-outcomes (PICO) format.[39] The review was registered with the Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42022310284).

Literature search was performed by two researchers using key word along with Boolean Operators, including Diabetes Mellitus OR T2DM OR T2D AND surfactant protein D OR SP-D OR pulmonary surfactant associated protein D AND oxidative stress OR oxidant of lipid peroxidation AND infection AND inflammation AND superoxide dismutase OR SOD AND malondialdehyde OR MDA. Search query was reformed according to the search criteria for each database.

The total number of articles retrieved was noted and duplicates were removed before screening. The searched literature was screened by two reserachers initially for identification of relevant full text of the studies that met the inclusion criteria. All relevant full-text articles were exported to Mendeley reference manager from the databases. Relevant articles were shared with rest of the co-authors and after discussion and consensus the relevant studies were included based on eligibility criteria and relevance to the topic for qualitative and quantitative syntheses. Total numbers of included and excluded articles were noted. Database search Excel sheets were managed separately for each data engine used for search.

The review included human studies providing data related to SP-D, risk of infection and oxidative stress in T2DM or role of SP-D in inflammation, published in peer-reviewed English-language journals. Original article/research with cross-sectional, case-control, cohort designs, correlational studies, randomised and non-randomised controlled trials with aims in line with the objectives of the current review were included. Studies that compared SP-D, MDA, SOD or infection rates between T2DM and control groups for quantitative synthesis were included. Animal studies demonstrating effect of oxidative stress on SP-D for qualitative synthesis were also included.

Poorly-written articles with flawed methodology, incomplete data and unclear outcomes, irrelevant data, articles with flawed statistics, systematic reviews, meta-analysis, and studies with subjects not matching the target population for the current review were excluded.

After identification of the included studies and discussion, data was extracted by two researchers. All extracted evidences were reviewed by the rest of the co-authors individually to minimise errors.

From the included studies, basic characteristics, like authors' name, year of publication, study design, setting, country, race, age, sample size (case and control), percentages of male and female participants, and sampling technique, if available, were extracted. Specifically, data related to infection rates, mean and standard deviations (SDs), confidence intervals (CIs) and significance ($p<0.05$) values for serum SP-D, MDA and SOD activity in T2DM and control groups was extracted. Data on the effect of oxidative stress on SP-D level was alone noted. From the extracted data, quantitative and qualitative evidence syntheses were done comparing the methodologies and results of the included studies. All extracted data was recorded in tabulated form on Excel sheets for backup, accuracy and to minimise errors for smooth review.

All the studies were reviewed for quality assessment using Joanna Briggs Institute Critical Appraisal Checklist (JBICAC).[40] The checklist points included were appropriate sample frame, appropriate sampling technique for enrolment of case and control, appropriate sample size, valid method for identification of condition with condition measured in the same way for all participants, and appropriate statistical analysis.

Quality of evidence was assessed using the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) tool keeping in view the limitations of the included studies, protocols for methodologies and selection criteria for the included participants, indirectness of evidence, inconsistency of results, and publication/ reporting bias.[41] To remove publication bias, studies with non-significant results were also included in the review as it is necessary to review negative studies to avoid under-estimation of harms and over-estimation of benefits.

Results

Of the 203 studies identified, 18(8.9%) were analysed; 16(89%)[1,3,5,22,26,32,37,42-50] quantitatively with humans as subjects and 2(11%)[24,25] qualitatively with animals as subjects (Figure). All the included articles in the review were of moderate to high quality (Table 1). With respect to quality of evidence assessed using GRADE tool, most of the studies described results well with mean, standard deviation and values of statistical significance, and the overall quality of evidence was moderate to high (Table 2).

Among the 16(89%) analysed quantitatively, 9(56.25%) were case-control studies, 1(6.25%) cohort, 2(12.5%) cross-sectional and 1(6.25%) observational, while the study design was not mentioned in 3(18.75%) studies. There were 5(31.25%) original articles, which were reviewed for SP-D, 4(25%), for MDA, 6(37.5%) for SOD activity, and 1(6.25%) study for both MDA and SOD activity.

Basic characteristics of the studies analysed quantitatively were noted and tabulated (Tables 3,6,7).

There were 5(31.25%) studies for SP-D, of which 4(80%) studies reporting significantly lower SP-D level in T2DM group than control group. Means are tabulated in Table 4. One (20%) study also demonstrated significant negative association of SP-D with HbA1c,while in 1(20%) study there was weak negative association of SPD with random blood

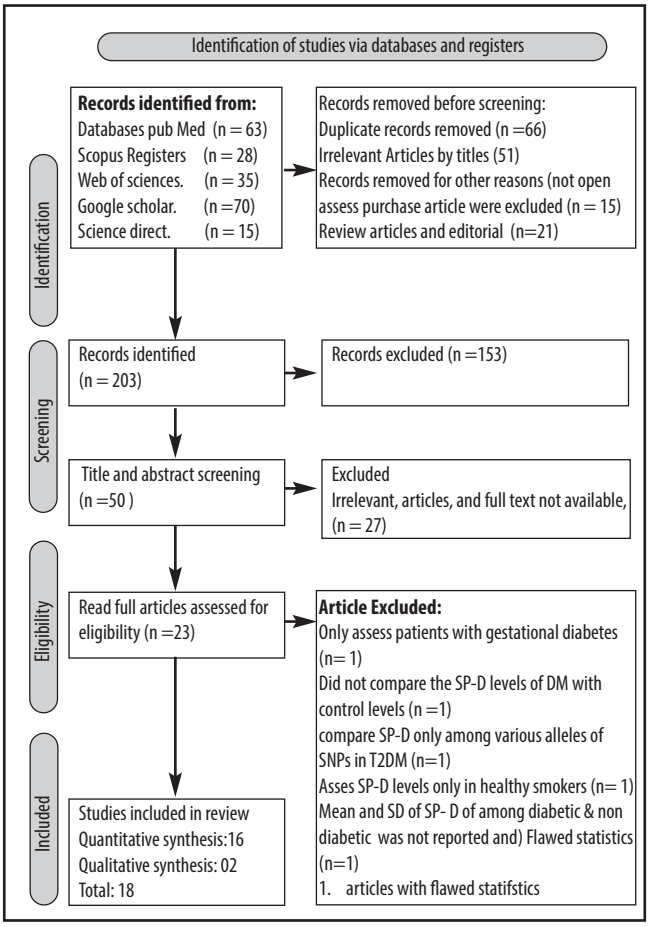

Figure: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart.

Table-1: Methodological quality assessment of eligible studies using Joanna Briggs Institute Critical Appraisal Checklist (n=46).

Authors and Year of Publication	Q1. Sample frame appropriate	Q2. Study sample appropriate	Q3. Sample size adequate	Q4. Study subject/ set ting	Q5. Data analysis conducted with sufficient coverage	Q6. Valid method for identification of condition	Q.7 Condition measured in the same way for all participants	Q.8 Appropria te Statistical analysis	Q.9 Response rate adequate/if not was the low response rate managed appropriately	Quality rating
Ghanayem et al.,2017[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Jawed el al 2015[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Fernandez- Real JM et al, 2010[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Jawed et al 2021[3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Lopez -Cano, et al., 2017[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Sharma et al,.2022[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Banik et al,, 2018[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Mishra et al,, 2017[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Kulaksizoglu et al,, 2016[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Nair, et al 2017[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Shang et al,, 2015[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Al-Rawi et al,, 2011[98]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Song et al,, 2007[48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Madi et al.,2016[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include
Briggs et al.,2016[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8Include
Tavares et al., 2019[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	8 Include

glucose (RBG), but it was not significant (p>0.05).Significant negative association between SP-D and FBG was reported by 2(40%) studies, while 1(20%) reported significantly higher SP-D levels in diabetic subjects compared to controls, and also reported positive correlation of SP-D with HbA1c and FBG, but the results were not significant (p>0.05) (Table 5).

Table-2: Quality assessment of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (n=16).

Author & year of Publication	limitation in the design	Inconsistency of results	Indirectness of evidences	Imprecision	publication bias
Ghanayem et al. 2017[22]	★	★	★	N/A	★
Jawed el al. 2015[5]	★	★	★	N/A	★
Fernandez-Real JM et al. 2010[26]	★★	★	★	N/A	★
Jawed et al. 2021[3]	★★	★	★	N/A	★
Lopez -Cano, et al. 2017[1]	★★	-	★	N/A	★
Sharma et al. 2020[42]	★	★	★	N/A	★
Banik et al. 2018[43]	★★	★	★	N/A	★
Mishra et al. 2017[44]	★★	★	★	N/A	★
Kulaksizoglu et al. 2016[45]	★★	★	★	N/A	★
Nair et al. 2017[37]	★	★	★	N/A	★
Shang et al. 2015[46]	★	★	★	N/A	★
Al-Rawi et al. 2011[49]	★★	★	★	N/A	★
Song et al. 2007[48]	★	★	★	N/A	★
Madi et al. 2016[32]	★	★	★	N/A	★
Briggs et al. 2016[47]	★★	★	★	N/A	★
Tavares et al. 2019[50]	★★	★	★	N/A	★

GRADE TOOL:[41]

The review findings start with a rating of ★★★★ grading low to high. Evidence can then be upgraded (addition of stars) or down-graded (or lose 'stars') based on the following:

1. **Limitation:** Two star (★=no limitation) enough sample size and proper selection of participants inclusion (case and control) criteria well defined and appropriate research methods to achieve goal
   One star (★) proper selection of participants and research methods to achieve goal, however small sample size was limitation or who did not mention p values (reporting bias)
2. **Inconsistency of results:** one star (★) no inconsistency and the results were in line with other previous studies
3. **Indirectness of evidences:** one star (★) if the participants of the study was according the goal of systematic review
4. **Publication bias:** one star (★) if no publication bias was found and there were studies with non-significant results (negative studies)
5. **Imprecision** was not applicable(N/A) as this was a systematic review, not a meta analysis.

There were 2(40%) studies showing lower SP-D levels in patients with infection. One of these studies reported significant lower levels of SP-D in T2DM subjects having extrapulmonary infections than without infections (94.3±58.6 vs 168±146.0 ng/ml; p=0002), and also reported that diabetic subjects had two times more risk of getting infections (odds ratio [OR]: 2.10, p=0.04 and 95% confidence interval [CI]: 1.01-4.35).[3] The other study found higher rates of recurrent respiratory infections in diabetic obese subjects compared to non-diabetic subjects (75% vs 26.6%, p=0.0002). Interestingly, this study reported significant lower SP-D levels in subjects with respiratory tract infections compared to subjects without respiratory tract infection. On multiple comparison by Tukey's post-hoc test, the said study found lower SP-D levels in diabetic obese subjects with recurrent respiratory tract infections compared to diabetic obese subjects without infections (67±26.7 vs 128±36.8 ng/ml, p=0.009), and similarly lower level was noted in non-diabetic obese subjects with recurrent respiratory tract infections than without infections (51±22.5 vs 125±50.9, p=0.001), suggesting that respiratory tract infections were linked to SP-D deficiency. The same study also documented that diabetic obese patients had a greater risk of recurrent pulmonary infections than non-diabetic obese (OR: 5.44; p=0.045) and non-diabetic normal-weight subjects (OR: 7.667; p=0.012).[5]

Table-3: Characteristics of the studies analysed for quantitative synthesis of surfactant protein -D in type 2 diabetes mellitus.

Author & Year year of publication	Data Collection Year	Study Design	Setting	Country & Race	Sample Size	Male (n)	Female (n)	Sampling Technique
Ghanayem et al., 2017[22]	2014 -2015	N/A	Menoufia University Hospitals Menoufia	Egypt	87	57	30	N/A
Jawed S el al., 2021[3]	2012	Case Control	Dow University of Health Sciences (DUHS), KHI	Pakistan	120	82	38	Non-Probability Convenient
Lopez -Cano C et al., 2017[1]	2015	Case Control	N/A	Spain White Population	147	N/A	N/A	N/A
Jawed S el al., 2015[5]	2011	Cross Sectional Study	National Institute of Diabetes & Endocrinology DUHS, KHI	Pakistan	90	N/A	N/A	Non-Probability Convenient
Fernandez- Real JM et al., 2010[26]	1998 -2005	Cohort	N/A	Spain Caucasian	333	137	196	Random Sampling Technique

Table-4: Comparison of surfactant protein-D (SP-D) levels among patients with type 2 diabetes mellitus (T2DM) and control groups in the studies analysed.

Author & Year year of publication	Diagnostic Method DM	Medium SP-D	Technique SP-D	SP-D (ng/ml) Mean ± SD		
				T2DM	Control	P value
Ghanayem et al.,2017[22]	N/A	Serum	ELISA	36.5±18.5	48.3±13.1	<0.001
Jawed S el al., 2021[3]	OGTT	Serum	ELISA	98.4±44.1	156±56.76	0.036
Lopez -Cano C et al., 2017[1]	N/A	Serum	ELISA	133.0 (35.4- 815.8)	97.6 (23.5 - 3362)	0.006
Jawed S et al., 2015[5]	OGTT	Serum	ELISA	128± 36.8	183±956.2	0.002
Fernandez- Real JM et al, 2010[26]	OGTT	Serum	ELISA	1.79 ± 0.15	1.88 ± 0.13	0.005

SD: Standard deviation, ELISA: Enzyme-linked ummunosorbent assay, OGTT: Oral glucose tolerance test.

There were 5(31.25%) studies that evaluated MDA levels in T2DM for quantitative synthesis. Higher level of serum MDA was noticed in the subjects with T2DM compared to control subjects in all the studies, but significant difference was reported by 3(60%) studies, non-significant by 1(20%), and not reported by 1(20%) study (Table 6).

There were 7(43.8%) that evaluated SOD, of total 3(42.9%) studies quantitatively that analysed SOD activity in T2DM, and revealed significantly lower SOD activity in T2DM

Table-5: Association of surfactant protein-D (SP-D) with glycated haemoglobin (HbA1c) and blood glucose random and fasting levels.

Authors & year of publication	Blood glucose (mgldl) Fasting (F) Random (R) Mean±SD			Glycated Haemoglobin (HbAlc) Mean± SD			SPD & HbA1c		SP- D & Blood glucose Fasting (F) Random (R)	
	T2DM	Control	*p*-value	T2DM	Control	*p*-value	*r*-value	*p*-value	*r*-value	*p*-value
Ghanayem et al., 2017[22]	247.7±89.2 (F)	88.4±7.2 (F)	<0.001*	8.4± 0.85	5.8 ± 1.3	<0.001*	- 0.282	0.008	−0.364 (F)	0.001*
Fernández-Real JM et al., 2010[26]	NA	NA	NA	N/A	N/A	N/A	N/A	N/A	−0.14 (F)	0.009*
Jawed S et al., 2021[3]	202±71.5 (R)	113± 67.98 (R)	0.0002*	N/A	N/A	N/A	N/A	N/A	0.017 (R)	0.15NS
Lopez-Cano C et al., 2017[1]	9.2±3.4 (F)	5.5±0.6 (F)	0.48 NS	8.0 ± 6.19	5.6 ± 6.04	0.001*	0.145	0.118 NS	0.118	0.16 NS

SD: Standard Deviation

Table-6: Comparison of malondialdehyde (MDA) level among patients with type 2 diabetes mellitus (T2DM) and control groups of the studies analysed.

Author & year of publication	Study Design	Setting	Country	Sample Size Control+ Pre-diabetes +T2DM	Age (years)	Medium MDA	MDA (µmol/L) Mean±SD		
							T2DM	Control	*p*-value
Sharma R et al.,2020[42]	Case Control study	Rama Medical College Hospital & Research centre, Kanpur	India	50+50+50	>30	Serum	3.94±1.02	1.93±0.31	N/A
Banik S et al., 2018[43]	Cross Sectional study	Noakhali Diabetic Hospital, Noakhali, Bangladesh	Bangladesh	60+0+90	28-70	Serum	5.38±1.64	2.63±1.63	<0.001
Mishra S et al., 2017[44]	Case Control study	Kalinga Institute of Medical Science, Bhubaneswar, Odisha, India	India	51+0+92	40 -65	Serum	uncomplicated 2.47±0.53 complicated 3.98±0.42	1.43±0.23	<0.05
Nair A et al., 2017[37]	case control	Outpatient Department of Oral Pathology and Microbiology, PMS College of Dental, Thiruvananthapuram	India	30+30	30-60	serum	0.77±0.15	0.35±0.09	p< 0.001
Kulaksizoglu S et al.,2016[45]	Case Control	N/A	Turkey	35+0+35	65-67	Serum	9.51±2.82	10.75±2.57	p>0.05 NS

SD: Standard deviation.

Table-7: Comparison of superoxide dismutase (SOD) activity among patients with type 2 diabetes mellitus (T2DM) and control groups of the studies analysed.

Author &Year	Study Design	Setting	Country	Sample Size T2DM+ control	Age range (years)	Sampling Strategy	Medium	Serum SOD Activity (U/mL)		*p*-value	Salivary SOD (U/mL)		*p*-value
								T2DM	Control		T2DM	Control	
Nair et al., 2017[37]	case control	OPD of Oral Pathology and Microbiology, PMS College of Dental, Thiruvanantha puram	India	30+30	30-60	N/A	Serum+ Saliva	1.37±0.2	1.16±0.2	< 0.001	1.57±0.2	1.39±0.18	< 0.001
Shang M et al.,2015[46]	N/A	N/A	China	28+40	N/A	N/A	Serum	72.27±18.81	117.06±15.63	N/A	N/A	N/A	N/A
Al-Rawi et al., 2011[49]	observati onal study	Al-Diwaniya Hospital	UAE	25+25	40-60	N/A	Serum & Saliva	1.48±0.53	1.09±0.18	<0.001	2.48± 0.94	1.12±0.27	NS
Song F et al., 2007[48]	N/A	N/A	China	113+92	N/A	N/A	Serum	36.86±8.16	30.54 ±.7.39	N/A	N/A	N/A	N/A
Madi M et al.,2016[32]	Case Control	Dental Sciences Institute South India	India	45+45	30-60 r	Convenient Sampling Technique	Serum	2.833±0.22 u/mg	4.315±0.0575	N/A	N/A	N/A	N/A
Briggs ON et al.,2016[47]	Case Control	N/A	Nigeria	109+73	N/A	N/A	Serum	48.30±24.16	57.24±16.23	0.003	N/A	N/A	N/A

subjects compared to the controls group. There were 3(42.9%) studies that reported significantly higher SOD activity in serum as well as in saliva of T2DM patients compared to the controls. There was 1(14.3%) study in which the difference was significant in serum SOD activity, but not significant in saliva. There was 1(14.3%) study that found higher serum SOD activity in T2DM compared to the control group, but did not mention value of significance, which means the finding might be subjected to reporting bias (Table 7).

There was 1(14.3%) study that compared SOD activity among control group, pre-diabetes (HbA1c 5.7- 6.4%) and 3 subgroups of T2DM (diabetic subjects with HbA1c <7%, HbA1c 79% and HbA1c >9%) and reported significantly higher SOD activity in T2DM subjects having HBA1c <7% compared to all other groups and subgroups, suggesting that higher SOD in T2DM subjects with boarderline HbA1c <7% is possibly an adaptive response to the increased oxidative stress. It also suggested that SOD activity decreased as glycaemic control worsened.[50] This study documented median and interquartile range (IQR) of SOD activity in control group was 1.67(1.39-1.93) U/mL, wherase in prediabetes was 2.23 (1.56- 2.74) U/mL. Median (IQR) of SOD activity in T2DM subjects with HbA1c <7% , HbA1c7 - 9% and HbA1c> 9% was 2.95(2.22 -3.55), 2.18(1.97- 3.34) and 2.38(1.97 -3.74) U/mL, respectively with significant p value of 0.004.[50]

With respect to qualitative synthesis done with 2(11%) studies, 1(50%) study demonstrated that hypochlorous acid (HOCl) was the major oxidant produced by myeloperoxidase (MPO)-hydrogen peroxide (H_2O_2)-halide system (MPO-H(2)O(2)-halide) during inflammation and adversely affected the aggregation property of SP-D by forming non-disulfide cross-linkage in its structure.[25]

There was 1(50%) study which demonstrated that excess generation of peroxynitrite (ONOO−) caused oxidative modifications in the oligomeric structure of SP-D. Formation of non-reducible, tyrosine-dependent cross-linkages due to nitration and cleavage of SP-D multimers by S-nitrosylation resulted in defective microbial aggregation.[24]

Discussion

The current systematic review was first to systematically evaluate the interesting hypothesis that the innate immunity as inferred from SP-D concentration is a crossroad of IR, T2DM, inflammation and infection.[26]

Studies from Egypt and Spain reported lower SP-D concentration in T2DM compared to non-diabetic subjects.[22,26] Compatible results were also reported from Pakistan.[3,5] However, conflicting results have also been reported.[1] The discrepancy might be due to induction of patients with long duration of T2DM subjects with at least 5-year follow-up period. The study[1] also reported significant negative association between SP-D and forced expiratory volume in first second (FEV1), which reinforced the knowledge that the long duration of T2DM results in pulmonary dysfunction and lung damage. Higher levels of SP-D in serum of these patients are due to transmigration of SP-D from alveoli to vascular compartments due to increased alveolar epithelial permeability caused by chronic inflammation, hence, high SP-D levels might reflect the lung damage.[1]

These findings might highlight one of the potential causes for the commencement and progression of pulmonary dysfunction in patients with T2DM, and suggested that SP-D could be a useful biomarker for lung function. The same study[1] recommended early screening of diabetic patients for lung disease to prevent progression of the diseases to lung damage. It also found positive correlation of HbA1c and FBG with SP-D[1], but the association was non-significant. On the contrary, other studies found significant negative correlation of SP D with FBG and HbA1c,[22,26,27] while one study reported weak and negative but non-significant association between SP-D and FBG.[3] The difference might have been owing to the difference in sample size.

In T2DM, abnormally high lipid peroxidation of polyunsaturated fatty acids through protein glycation and eventually rise in malondialdehyde (MDA) level is evident. However, body is not adapted to form sufficient anti-oxidant enzymes to cope with oxidative stress.[33,34] A significantly higher serum MDA level in Indian and Bangladeshi T2DM patients than control groups was documented by most of the studies analysed.[37,42-44] Contrary to these studies, a Turkish study did not find any significant difference for the MDA level among T2DM and control groups.[45]

The current review observed a significantly lower level of SOD in patients with T2DM than controls in 3 studies.[46,47] The possible key reason for declined SOD activity is the glycosylation of Copper, zinc superoxide dismutase (Cu, Zn-SOD) which could lead to enzyme inactivation both in vivo and in vitro.[51] Studies conducted in India and the United Arab Emirates (UAE) reported discordant results and documented significantly higher serum and salivary SOD activity in diabetic subjects compared to the control group.[37,49] Concerning salivary SOD, Nair, et al. showed significant difference, while Al-Rawi's results were not significant.[37,48] Al-Rawi explained that the increased production of free radicals may have enhanced the

antioxidant defence system which counter-balanced the pro-oxidant environment in diabetic subjects.[49] A Chinese study also reported higher levels of serum SOD in T2DM compared to the control group.[1,48] Tavares et al. reported higher SOD activity in T2DM individuals having borderline HbA1c <7 than the control group, suggesting that the increase in SOD activity was adaptive response to the initiation of oxidative stress. However, the SOD activity declined with worsening diabetic control, and showed lowest SOD acivity in T2DM subjects having HbA1c >9%, reflecting the presence of oxidative stress.[50]

The current literature search did not yield any quantitative study that reported the association of MDA level and SOD activity with SP-D, but two qualitative experimental animal studies were found which reported that oxidative stress suppressed the function of SP-D, especially its aggregation activity of pathogens, by altering its structure and formation of non-disulphide linkages in its structure. Disulphide linkages have vital role in stabilising its structure which is required for its full function and host defence.[24,25]

Although all the studies analysed currently tried to sort out the link involving SP-D, infections and oxidative stress in T2DM, but no conclusive findings could be established. The current review has opened new horizons for researchers to work at the molecular level to establish this association.

The current systematic review has its limitations. It minimised the risk of publication bias by including negative studies with non-significant results, but it would have been better to check publication bias by Egger's linear regression test, funnel plot or any other statistical test.

The strength of the review is that it assessed the quality of the studies using JBICAC, and quality of evidence using GRADE, which allowed it to identify gaps in existing knowledge.

Conclusion

SP-D, oxidative stress, inflammation and infections were found to be linked to each other for the pathogenesis of infections in T2DM. Collective findings of most of the included studies concerning SP-D suggested that deficiency of T2DM was the possible cause of the high risk of infections, while the studies concerning oxidative stress in T2DM suggested that oxidative stress was a major pathway for infections. But the actual link between these parameters was not yet clear.

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SJ and BA: Conceived idea, literature search and data extraction, writing, PROSPERO registration.

MM: Involved in conceiving idea, guidance for PRISMA protocols, literature search PROSPERO registration, review and revision.

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