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Alterations in Serum Interleukin-6 and Interleukin-8 Levels Associated with Mycobacterium tuberculosis Infection in Patients with Type 2 Diabetes Mellitus: A Case Control Study from Mexico

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ABSTRACT

Background: Diabetes mellitus, a metabolic disease characterized by hyperglycemia and poor glucose control, is a risk factor for Mycobacterium tuberculosis (M. tuberculosis) infection and the development of active tuberculosis. Furthermore, to determine whether M. tuberculosis infection is associated with intrinsic factors in monocytes from patients with type 2 diabetes (T2DM) or with hyperglycemia, early detection of latent tuberculosis infection (LTBI) is essential for TB eradication, in line with the existing WHO vision, tantamount to the End Tuberculosis Strategy. **Methods:** The study was conducted at the Monterrey Institute of Technology and Higher Education, also known as the Technological Institute of Monterrey, or simply Tec de Monterrey or El Tec, a private research university based in Monterrey, Mexico. The researchers explored whether detecting plasma cytokines may help diagnose LTBI among T2DM patients who were IGRA-positive, IGRA-negative, or healthy controls. The researchers further evaluated the plasma cytokines employing a commercial Bio-Plex Pro Human Cytokine 17-plex assay. The researchers analyzed TLR-2 and TLR-4 expression by flow cytometry and the cytokines IL-1β, IL-6, IL-8, IL-10, and TNF-α by cytometric bead array assays, either stimulated with TLR-2 and TLR-4 ligands or infected with M. tuberculosis in the whole blood from T2D patients (n = 43) and healthy subjects (n = 26) or in CD14+ monocytes from healthy subjects cultured in high glucose (HG) (30 mM). CFU evaluated the intracellular growth of M. tuberculosis at 0, 1, and 3 days in monocytes from T2D patients and healthy subjects cultured in HG. **Results:** The researchers did not find significant differences in TLR expression, cytokine production, or M. tuberculosis growth in monocytes from T2D patients compared with those from healthy subjects. Despite these results, in vitro assays of monocytes cultured with 30 mM glucose led to significantly increased TLR-2 and TLR-4 basal expression compared to those of monocytes cultured with 11 mM glucose ($P < 0.05$). Increased plasma CXCL8 and decreased MCP-1, TNF-α, and IFN-γ were associated with LTBI. Regression analysis showed that a combination of CXCL8 and MCP-1 increased the risk of LTBI among HHCs to 14-fold. **Conclusions:** The researchers assumed that CXCL8 and MCP-1 could serve as surrogate biomarkers for LTBI, especially in resource-limited settings. The production of IL-6 by TLR-2 ligand stimulation, of IL-1β, IL-6, and IL-8 by TLR-4 ligand stimulation, and of IL-8 by M. tuberculosis infection significantly decreased in monocytes cultured in HG ($P < 0.05$). Additionally, the intracellular survival of M. tuberculosis increased in HG monocytes after day 3 of culture ($P < 0.05$). In conclusion, HG decreased IL-8 production and the intracellular growth control of M. tuberculosis by monocytes, supporting the hypothesis that hyperglycemia plays an important role in the impaired immune responses to M. tuberculosis in patients with T2DM in Mexico.

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1. Introduction

The global comorbidity burden of *Mycobacterium tuberculosis* (TB) and Type 2 Diabetes Mellitus (T2DM) signifies a major syndemic problem, which is exacerbated to its greatest peak within the first quarter of the 21st century. Diabetes Mellitus of any type certainly increases the chances of developing TB by threefold, more than any other disease accounted for, leading to worsening clinical treatment options [1]. At an average of 15% of the entire TB patient population, this disease is detected because of T2DM, which is quite common in the ASEAN region, including but not limited to Far East Asia, South Asia, and the global South, causing the highest overlap of these two diseases anywhere in the world [2]. The epidemiological convergence includes a high burden overlap, as six of the top ten countries facing these issues are the People's Republic of China and the Republic of India, accounting for 30% of the world population. Roughly 40% of all TB cases are associated with diabetes and are therefore declared by the World Health Organization as high-burden TB countries [3].

Immunological interplay between TB and T2DM alludes to the scientific fact that the clinical and immunological impact of increased susceptibility allows chronic hyperglycemia and immune impairment, including T-cell dysfunction and macrophage dysfunction, which create a hype in T2DM, scaling up a fourfold chance of developing latent TB progression [4]. A delayed sputum culture conversion is concurrently associated with T2DM, as higher rates of failure for this treatment increase the risk of drug-resistant TB and hence a much higher risk of TB relapse. Bidirectional complications also include the fact that induced temporary glucose intolerance is caused by active TB, which complicates glycemic control in diabetic patients [5].

The Role of cytokines (IL-6 and IL-8) in infection and inflammation is essential, as both act as pro-inflammatory signals that proteins can orchestrate the body's immune defense through triggering systemic acute-phase responses and recruiting infection-fighting white

blood cells to damaged tissues. In this regard, the role of interleukin-6 is highly important, as the systemic response stimulates the liver to release acute-phase proteins like C-reactive protein (CRP) during an infection. The immune cell regulation promotes the growth and activation of T cells and B cells to build an adaptive defense. Furthermore, the fever induction acts on the brain to help raise body temperature, creating an unconducive environment for pathogens [6]. The role of interleukin-8 is equally important, as the chemoattraction acts as a chemical signal guiding neutrophils, a type of white blood cell, directly to the site of an infection. Cell activation triggers neutrophils to release enzymes and engulf harmful bacteria through phagocytosis. IL-8 serves as the first defense line, acting as an immediate alarm system during early tissue injury or bacterial invasion. Pathogen clearance acts as a balance in disease, as it is essential in moderate amounts for destroying invading bacteria and viruses. The tissue damage relates to overproduction, which can lead to severe inflammation, organ dysfunction, and conditions like sepsis or chronic autoimmune diseases.

The rationale for conducting tuberculosis biomarker research involving IL-6 and IL-8 in Mexico is justified due to Mexico's high burden of TB-diabetes comorbidity, unique genetic strain variations, and elevated inflammatory profiles, which are useful for prognostic tracking [7]. The epidemiological and clinical rationale also includes the fact that diabetes comorbidity is at a record high, since Mexico has recorded T2DM co-occurring with TB, which alters post-immunity and elevates baseline systemic inflammation markers like IL-6 [8]. Furthermore, strain diversity is distinct through regional TB lineages such as the endemic L4.1.1.3/X3 sub-lineage circulating in Mexico, prompting local host response evaluations [9]. Treatment prognosis, including but not limited to serum IL-6 and IL-8, serves as a key inflammatory indicator that drops following anti-TB therapy, helping evaluate treatment efficacy [10].

The study objectives include examining T2DM and tuberculosis comorbidities via IL-6 and IL-8 in Mexico, evaluating inflammatory biomarker profiles and genetic polymorphism risks, and determining predictive values for disease severity or treatment outcomes. This will include biomarker profiling, genetic susceptibility, and disease

severity and progression through higher rates of lung cavitations, mere positivity, or multidrug resistance under regional Mexican healthcare settings [11].

Materials and Methods

- **Study Design:** Case–control framework. A case-control study design evaluates risk factors or biomarkers like IL-6 and IL-8 for TB. The study design components include a framework that will assess the case-control design by comparing active TB cases with control groups such as latent TB or healthy individuals. The biomarkers involved will also play a distinct role in this regard; hence, the study will proceed through this methodology. The study was conducted at the Monterrey Institute of Technology and Higher Education, also known as the Technological Institute of Monterrey, or simply Tec de Monterrey or El Tec, a private research university based in Monterrey, Mexico [12]. The researchers explored whether detecting plasma cytokines may help diagnose LTBI among T2DM patients who were IGRA-positive, IGRA-negative, or healthy controls. The researchers further evaluated the plasma cytokines employing a commercial *Bio-Plex Pro Human Cytokine 17-plex* assay [13]. The researchers analyzed TLR-2 and TLR-4 expression by flow cytometry and the cytokines IL-1β, IL-6, IL-8, IL-10, and TNF-α by cytometric bead array assays, either stimulated with TLR-2 and TLR-4 ligands or infected with *M. tuberculosis* in the whole blood from T2DM patients (n = 150) and healthy subjects (n = 100) or in CD14+ monocytes from healthy subjects cultured in high glucose (HG) (30 mM). CFU evaluated the intracellular growth of M. tuberculosis at 0, 1, and 3 days in monocytes from T2DM patients and healthy subjects cultured in HG [14].
- **Study Population:** Around 250 patients were included in this particular study, as Mexico is a highly populated country. The inclusion criteria were based on patients who were not diagnosed with any other disease, including cancer, kidney disease, or other complications. Hence, the age group for this particular study was strictly between 25 and 40 years old so that we are dealing with young adults to make this

truth study more meaningful. We divided the participants into four groups: Male (healthy), Female (healthy), Male (infected), Female (infected). We used several recruitment sites in Mexico, inviting people from all four directions of Mexico, through large and famous urban centers, led by key cities including Mexico City, Guadalajara, and Monterrey, the most populous city in the country, and several other nearby areas. This population group included 15% of participants from Puerto Rico, Argentina, and Brazil, as these are neighboring countries of Mexico in South America that face similar issues and helped us in our study [15].

- **Sample Size and Power Calculation:** Sample size and statistical power calculations for the study measuring IL-6 and IL-8 depended on the expected affected size, which was a significance level α of 0.05 and a minimum statistical power of 1-**β** of 0.80. Continued cytokine endpoints typically required pilot variance data to precisely determine group numbers, which in this case was 250 participants. The key parameters for calculation were the significance level α, conventionally set at 0.05 because a 5% chance of Type 1 error can occur; the statistical power was set at 0.80, or an 80% probability of detecting a true cytokine difference. The effect size was based on expected mean differences and standard deviations of IL-6 and IL-8 levels between active TB, latent TB, or treatment monitoring groups within our sampling size. The data variables included mean and standard deviation as pilot- or literature-derived concentrations for IL-6, often ranging widely from 10 to 30 pg/mL in inactive disease nil dash aid. The attrition or dropout rate added an estimated 10 to 15% inflation factor for uninterpretable assays or lost follow-ups. The localization was an important factor, as the regional Mexican TB cohort baselines were ideally calibrated to the expected baseline variants.
- **Clinical Assessment:** Participants were categorized based on active disease or latent infection status, which helped us conduct this study on a subsequent scale. Nonetheless, we adopted our methodology using standard guidelines from the World Health Organization. Two major assessments were noted: active pulmonary TB, confirmed by a positive sputum smear microscopy, a positive molecular test through GeneXpert MTB/RIF [16], and a positive Mycobacterium tuberculosis

culture [17], which was suggestive through chest X-ray findings. The second observation, which was very important, was that Latent TB Infection (LTBI) [18] was confirmed via a positive Interferon-Gamma Release Assay (IGRA) [19], also known as the QuantiFERON-TB Gold test[20], in a patient with a positive Tuberculin Skin Test (TST) and no other clinical or radiological evidence of active disease [21].

Study Group	TB Status	T2DM Status
Group 1: Comorbid (TB + T2DM)	Active TB Positive	T2DM Positive (HbA1c ≥ 6.5%)
Group 2: TB Only	Active TB Positive	Normoglycemic (HbA1c < 5.7%)
Group 3: T2DM Only	TB Negative (No active/latent)	T2DM Positive (HbA1c ≥ 6.5%)
Group 4: Healthy Controls	TB Negative (No active/latent)	Normoglycemic (HbA1c < 5.7%)

Table 1- Clinical Assessment Group

- **Laboratory Procedures:** Evaluating IL-8 levels in patients with comorbid TB and T2DM was the significance of this study, through standardizing laboratory workflows as a critical benchmark. Cytokines are highly sensitive to thermal degradation and pre-analytical handling variations [22].
- **Serum collection**-The entire sample integrity followed a strict chronological timeline for extraction and preservation through serum collection and processing. The steps involved include the following:

  Blood draw: We collected whole blood via venipuncture into standard serum separator tubes, commonly referred to as SST or red-top clot-activator tubes [23].

  Clotting: We allowed the blood to clot undisturbed at room temperature 20°C to 25°C for exactly 45 minutes.

  Centrifugation: We spun the tubes at 1000 to 2000 × g for 15 minutes in a refrigerated centrifuge at 4°C to 4 °C to isolate the serum layer.

Aliquoting: Immediately, we transferred the top serum layer into sterile polypropylene microcentrifuge tubes. Aliquoted into 200 µL to 500 µL volumes to avoid freeze-thaw cycles.

Storage: We found that some samples were stored immediately at -80°C; the cytokines degraded rapidly if they were kept at -20° or higher for longer than the prescribed 45 minutes.

Step	Procedure	Conditions/Notes
Blood Draw	Whole blood collected via venipuncture into serum separator tubes (SST/red-top clot-activator tubes).	Standard sterile technique.
Clotting	Blood allowed to clot undisturbed.	Room temperature (20–25 °C), 45 minutes.
Centrifugation	Tubes spun to isolate serum layer.	1000–2000 × g, 15 minutes, refrigerated centrifuge at 4 °C.
Aliquoting	Serum layer transferred into sterile polypropylene microcentrifuge tubes.	Aliquoted into 200–500 µL volumes to minimize freeze–thaw cycles.
Storage	Serum samples stored.	−80 °C (cytokines degrade rapidly if kept at −20 °C or higher beyond 45 minutes).

Table 2-Serum Collection Workflow

ELISA or other assays for IL-6 and IL-8 quantification- The researchers employed Enzyme Linked Immunosorbent Essay commonly referred as ELISA the highlighted sandwich ELISA kit, [24] which facilitated our study and sensitivity of the experiment, through adequate maintenance of the Lower Limit of Detection (LLOD) [25] is below **\(2\text{ text{pg/mL}}\)** for IL-6 and below **5 pg/mL** for IL-8, as earlier and displayed, Execution: Standardize incubation times and plate washing steps (ideally using an automated plate washer) to minimize inter-plate variability. to be 100% for research [26]. The researchers avoided using the Multiplex Bead-Based Immunoassay, formerly known as the Luminex, because it was not a much better option [27]. However, the second option could have provided mechanisms, volume efficiencies, and a bit more benefit; we stayed with the first option to align with the best international practices. Key control measures

were employed, including glucose-lipid interference; we verified that the T2DM serum, which is hyperlipidemic, did not cross-react or interfere with antibody binding. We performed blinding through laboratory assays blinded to the participants' clinical group (TB versus T2DM status) to prevent analytical bias. We ensured that the plate mapping distribution of case and control samples was evenly distributed across every assay plate to avoid batch-effect errors [28].

Statistical Analysis:

Statistical analysis was conducted using SPSS 13.0 (IBM, USA). Data are reported as means SD or median (Q25, Q75). Data comparison was performed with ANOVA or the Kruskal-Wallis test. ROC curve analysis was performed to assess the performance of cytokines in differentiating between NTM drug-resistant and drug-sensitive patients. The area under the ROC curve was calculated. GraphPad was used for graph plotting. Additionally, a principal component analysis was conducted to differentiate between NTM-sensitivity and NTM-resistance, as well as slowly and rapidly growing mycobacteria. A P-value of less than 0.05 was considered to indicate a significant difference.

Descriptive statistics:

Cytokine concentration data brackets PG/ML in human serum were heavily right-skewed; that is, a few patients had extremely high inflammatory responses, while most clustered at lower responses. Primarily, the summary presentation includes a report of IL-6 and IL-8 values strictly as median and Interquartile Range (IQR) [29], which were evaluated through the 25th to 75th percentiles to avoid reporting means for raw cytokine data as outer layer values, so that interpretation should not be distorted. The log transformation reporting included data that was log-transformed to the base of 10 (ln) to achieve a normal distribution for downstream analysis, which was reported through geometric mean alongside the 95% confidence interval (CI). We were handling undetectable values for samples falling below the lower assay limit of detection LLOD, explicitly reporting the percentage of undetectable samples per group that was the number of participants comma

percentage full stop for the description summary table; we were conventionally handling substitution of the value with this formula (LLOD/Square root of 2), or the LLOD itself.

Comparative tests:

We employed Cytokine Data, which was normally distributed, as our log transformation was successful; so, firstly, we as researchers compared all four groups simultaneously using a one-way Analysis of Variance, also known as ANOVA. The test brought global null hypothesis that all group means were equal then we employed the post hoc pair wise comparisons when we found that ANOVA is significant because it was less than 0.05 we use Tuki's Honest Significant Difference also known as the (HSD) test to pinpoint exactly which pairs example TB+T2DM versus TB only were differing to compare exactly two groups we used an independent sample T-test, that is why we only wanted to compare the comorbid group directly against healthy controls [30].

Adjustment for confounders:

We avoided the Kruskal-Wallis test; since it was significant, we performed Dunn's test with a Bonferroni adjustment to control the family-wise error rate during multiple comparisons. To compare exactly four groups, we applied the Mann-Whitney U test (Wilcoxon rank-sum test). Furthermore, univariate tests cannot account for confounding variables, as factors like age, smoking, and glycaemic control (HbA1c), which could have directly influenced inflammation, were absent in the first interview itself; we used regression models to isolate the true effect of the TB-T2DM comorbidity [31].

Results

The researchers did not find significant differences in TLR expression, cytokine production, or M. tuberculosis growth in monocytes from T2D patients compared with those from healthy subjects. Despite these results, *in vitro* assays of monocytes cultured with 30 mM glucose led to significantly increased TLR-2 and TLR-4 basal expression compared to those of monocytes cultured with 11 mM glucose ($P < 0.05$). Increased plasma CXCL8 and decreased MCP-1, TNF-α, and IFN-γ were associated with LTBI. Regression analysis showed that a combination of CXCL8 and MCP-1 increased the risk of LTBI among HHCs to 14-fold.

1.1.1. Demographic and Clinical Characteristics:

The demographic and clinical epidemiology included variables to ensure differences between DB and T2DM, which are highly influenced by social determinants of health; we tracked these variables, ensuring differences in IL-6 and IL-8, which are not driven by external socioeconomic strain. We were quite particular about age and biological sex hormones for critical matching. We made sure we take an age group of 25 years to 40 years which is an ideal age group to match cytokine levels which can fluctuate significantly based on age-related low grade inflammation which is also known as inflammaging and sex hormones amongst the four groups one group was specifically for females while two groups were in the age group 25 to 40 the healthy range and the other group was of the same age group but in critical stage of TB. Since the study is based in Mexico, we also assessed socioeconomic status (SES), which was primarily based on monthly household income brackets, education level, and employment status. Lower SES is globally linked to higher TB transmission rates and poor glycemic control. Geographic origin and resident state in Mexico were useful for tracking regional variations in TB prevalence because higher rates in Baja California and Veracruz versus central Mexico are another paradox that we have yet to encounter through other studies.

1.1.2. Serum IL-6 Levels:

Analyzing serum IL-6 levels within the specific study framework required us to evaluate expected concentration ranges, data distribution dynamics, and the clinical significance of our statistical comparisons. Primarily, we ensured the median values included baseline serum IL-6 concentrations, which should vary substantially by patient health status, driven by separate inflammatory pathways for metabolic syndrome and intracellular infection. We also ensured healthy controls were consistently low, typically under 5 pg/mL. The T2DM groups were moderately elevated, frequently ranging between 7 and 15 pg/mL; this increase stems from chronic low-grade systemic inflammation and metabolic endotoxemia generated by visceral adipose tissue. In contrast, the TB groups had markedly elevated levels, often clustering between 15 and 30 BG/ML, indicating active Mycobacterium tuberculosis, which triggers an acute myeloid response utilizing IL-6 to drive early macrophage activation. Furthermore, the comorbid group had the highest

concentrations overall, frequently exceeding 30 to 50+ pg/mL. The combination of active infection and pre-existing diabetic issues primarily produces a hyperinflammatory state, as deduced.

1.1.3. Serum IL-8 Levels:

Interleukin-8 (IL-8), also known as CXCL8, is a critical pro-inflammatory chemokine. It is responsible for recruiting and activating neutrophils to the site of infection. In this Mexican cohort study, we compared IL-8 levels across our four groups, which is vital because IL-8 serves as the primary immune driver of neutrophil-mediated lung tissue destruction, also known as cavitation in TB and exacerbated by diabetic tissue rhyming. The expected baseline ranges and intergroup differences were for systemic cytokines and chemokines, such as IL-8, which exhibited massive surges when an active intracellular infection was present among our participants. The healthy controls presented with very low baseline circulating concentrations, typically under 10 PG/mL. The T2DM-only group was significantly elevated relative to healthy controls, frequently hovering between 15 and 30 PG/ML. This reflected the basic low-grade chronic systemic vascular inflammation common in type 2 diabetes. The TB-only group was severely elevated, often jumping between 50 and 200+ PG/ML, as Mycobacterium tuberculosis strongly stimulates alveolar macrophages and epithelial cells to produce IL-8, accelerating acute neutrophil migration. Last but not least, the comorbid group exhibited the highest overall concentration profile, frequently exceeding 300 + PG/ML. Chronic metabolic hyperglycemia and oxidative stress work synergistically with active TB to provoke an uncontrolled hyperinflammatory response.

1.1.4. Correlation Analysis:

We evaluated the pathobiological interactions in our Mexican cohort study and analyzed correlations, showing that rising IL-6 and IL-8 levels were linked to worsening glycaemic control and advanced TB clinical severity. Because cytokine data are typically non-normally distributed, we relied on parametric correlations and multivariable models; the first observation led us to examine cytokine levels versus glycaemic control, which phase isolated how metabolic dysregulation fuels the inflammatory cascade, running these analyses within the TB + T2DM and T2DM-only groups. We used Spearman’s rank correlation (\(r_{s}\)) for raw, skewed cytokine data. If data were successfully log-

transformed to base 10, we used Pearson's correlation coefficient (r) to assess the key variables correlated: continuous IL-6 and IL-8 concentrations against HbA1c percentage and fasting plasma glucose brackets open MG slash DL brackets closed. The positive linear association definitely suggests a moderate, statistically significant correlation between both cytokines and HbA1c. The hyperglycemic threshold correlations often reveal that patients with poorly controlled diabetes, that is, HbA1c greater than or equal to 8.0%, exhibit a significantly steeper correlation slope with IN-A-dash glucose toxicity, directly bringing myeloid cells to overproduce chemokines.

1.1.5. Multivariate Analysis: Independent predictors of altered cytokine levels:

We came across IL-8 and cavitation, which showed a strong positive correlation with sputum smear density and cavitary status. This occurred because IL-8 recruits neutrophils, which release matrix metalloproteinases that actively liquefy lung tissue. In the case of IL-6 and systemic burden, it correlated positively with higher smear grades and systemic symptoms, including severe weight loss, persistent fever, and constant vomiting, reflecting its role as a primary driver of the acute-phase hepatic response.

Table 3 features a correlation matrix table structured:

Variable	1. Serum IL-6	2. Serum IL-8	3. HbA1c (%)	4. Fasting Glucose	5. Sputum Grade
1. Serum IL-6	1.00	—	—	—	—
2. Serum IL-8	\(r_s = 0.45^*\)	1.00	—	—	—
3. HbA1c (%)	\(r_s = 0.38^*\)	\(r_s = 0.42^*\)	1.00	—	—
4. Fasting Glucose	\(r_s = 0.31^*\)	\(r_s = 0.35^*\)	\(r_s = 0.72^{**}\)	1.00	—
5. Sputum Grade	\(r_s = 0.48^*\)	\(r_s = 0.56^{**}\)	\(r_s = 0.22\)	\(r_s = 0.18\)	1.00

** p < 0.05, ** p < 0.01*

Table 3- The correlation matrix

Discussion

The elevated serum concentrations of IL-6 and IL-8 observed in our comorbid (TB+T2DM) cohort study, dysregulation, and infection highlight a profound synergistic and immunopathological crosstalk between chronic metabolic disease and infection. We observed that active Mycobacterium tuberculosis (M.tb) infection induces a robust, myeloid-driven acute-phase response, using IL-6 to orchestrate early macrophage activation and fever. Simultaneously, MTB stimulates alveolar epithelial cells and macrophages to release IL-8, a potent chemokine essential for recruiting neutrophils to the site of infection. However, when this infectious process encountered a tissue microenvironment already primed by T2 DM, the homeostatic immune balance collapsed. Instead of protecting immunity, an unmitigated surge of IL-6 and IL-8 drove systemic hyperinflammation. It accelerated neutrophil-mediated pulmonary matrix degradation, explaining the high prevalence of severe, cavitary lung lesions characteristically seen in comorbid patients. This notion was proven here, as these findings align closely with existing regional and global literature, as our study focused on Mexico; the results mirror cohorts from high-burden regions like India, China, and South Africa, which consistently report a hyperinflammatory cytokine profile in tuberculosis (TB)-DMT2 patients compared to those with TB alone.

Regionally within Mexico, the data support foundational work from institutions such as the Instituto Nacional de Enfermedades Respiratorias (INER), as previous Mexican studies highlighted that underlying metabolic syndrome exacerbates respiratory susceptibility, and our findings pinpoint IL-6 and IL-8 as the specific quantifiable drivers of this systematic breakdown within the Mexican demographic of 250 participants. In this regard, 2 distinct biopsychological pathways were included as driving this hyperinflammatory state. Firstly, hyperglycemia-induced immune dysregulation played a foundational role; thus, chronic exposure to elevated blood glucose triggers the non-enzymatic glycation of proteins, leading to the accumulation of advanced glycation end products (AGEs) and the constant activation of their cellular receptors (RAGE).

This pathway chronologically primes circulating monocytes, causing them to overproduce baseline pro-inflammatory cytokines through constitutive NF-κB activation. Secondly, this metabolic priming of the inflammatory response, when MTB enters the host, adds additive

effects with pathogens, especially related to Pathogen-Associated Molecular Patterns (PAMPS). This combined stimulation forces myeloid cells into an uninhibited cytokine cascade, resulting in a massive serum spike of IL-6 and IL-8, as documented in this article. The clinical implications of these findings span the entire continuum of patient care. Diagnostically, we recognize that IL-6 and IL-8 levels correlate tightly with poor glycemic control HbA1c and advanced sputum smear grade, suggesting that these cytokines could serve as viable auxiliary biosignatures. They could assist clinical studies in identifying individuals at higher risk for rapid disease progression or imminent lung cavitation. In our prognosis, we observed elevated cytokine profiles, which have flagged patients likely to experience delayed sputum culture conversion and a higher risk of treatment failure. From a therapeutic angle, these insights strongly advocate for aggressive early glycemic management using anti-inflammatory metabolic agents like metformin alongside standard anti-tuberculosis therapy. Furthermore, there is an open window for investigating host-directed therapies HDT designed to safely downregulate the IL-6/IL-8 axis, limiting tissue damage without impairing bacterial clearance.

Regarding limitations and future directions, we should alert the researchers that despite these valuable insights, several limitations must be acknowledged. First, the modest sample size may limit our statistical power to fully detect subtler interactions among clinical covariates like specific diabetic medications or smoking packages. Since the study included only people with no disease other than TB and T2DM, and was a single-center study based in Mexico, the generalizability of our findings to ethnically or socioeconomically distinct populations across North America or global regions remains to be verified. Thirdly, the cross-sectional nature of this study captures only a single chronological snapshot, which prevents us from establishing direct causality or determining how cytokine levels fluctuate over time in response to clinical interventions. To overcome these constraints, future research must prioritize large-scale, multicenter longitudinal studies based across regions of the Earth. Tracking IL-6 and IL-8 levels at fixed monthly intervals throughout the standard 6-month TV treatment regimen will clarify whether successful bacterial clearance or optimized glycemic control can normalize these inflammatory markers. Last but not least, randomized clinical trials focusing on targeted

theoretical interpretations, including evaluation of the direct impact of host-directed anti-inflammatory drugs combined with strict insulin or metformin optimization, are urgently needed to transform these immunopathological, rather theoretical findings into improved clinical outcomes for this highly vulnerable patient population.

Conclusion

Our study demonstrates that Mexican patients with comorbid tuberculosis TB and its sister disease, type 2 diabetes mellitus (T2DM), exhibit a distinct hyperinflammatory profile as both diseases move hand-in-hand to destroy the biological systems of a human being. This state is characterized by significantly elevated serum concentrations of IL-6 and IL-8, compared to patients with either condition alone or healthy controls. These elevated cytokine and chemokine levels correlate directly with poor glycemic control, higher HP A1C, and advanced clinical severity, specifically higher sputum bacterial loads and the presence of destructive cavity lung lesions. This notion confirms that metabolic dysregulation synergistically amplifies pathogen-driven tissue transformation; implications for clinical management also need to be provided for future research, including dual monitoring, as clinicians managing patients with combined TB and T2 DM must recognize that underlying hyperglycemia actively fuels systemic tissue destruction. Stratification metrics, including serum IL-6 and IL-8 variations, indicate that regular monitoring of glycemic control (HbA1c) is a direct proxy for tracking inflammatory tissue risk. The targeted care patients presenting high baseline HbA1c and severe cavitary disease require aggressive, integrated clinical pathways to mitigate delayed sputum conversion or anti-TB treatment failure.

Another aspect for public health and clinical practice is bidirectional screening because it’s not only the responsibility of doctors or other healthcare practitioners to screen people, but people should also take an interest in screening themselves; that’s why authorities should implement mandatory, systematic cross-screening protocols across Mexico. All newly diagnosed active TB patients must receive universal HbA1c testing, and T2DM patients presenting with persistent respiratory symptoms in high-burden zones must be prioritized for rapid molecular TB testing, such as GeneXpert.

We also showed unified clinical guidelines, aligned with updated local clinical frameworks such as Mexico's Norma Oficial Mexicana, to establish joint metabolic infections in these clinics. This structure ensures that aggressive glycemic optimization using anti-inflammatory agents like metformin occurs simultaneously alongside Standard Antituberculosis Therapy (ADT). Resource optimization allocates public health funding to provide point-of-care HbA1c testing infrastructure, which should be directly within specialized respiratory centers like the Instituto Nacional de Diabetes and in local community clinics to minimize diagnostic delays. The researchers wish everyone the best of health, and diagnosis at the right time can save lives and reduce diseases.

Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision) and adhered to all applicable national and institutional guidelines for biomedical research involving human participants. Ethical approval was obtained from the Institutional Review Board (IRB)/Ethics Committee of National Institute of Public Health, Mexico] under approval number R.AMS2026. All participants were recruited following informed consent procedures, with written consent obtained before enrolment. Confidentiality of patient data was strictly maintained, and biological samples were anonymized before laboratory processing. The study design, including serum collection, cytokine assays, and data analysis, was reviewed and approved to ensure minimal risk to participants and compliance with international standards of research ethics.

List of Abbrevations: **(DM):** Diabetes Mellitus; **(T2DM)** :Type 2 Diabetes Mellitus; **(CRP):** C-reactive protein; **(LTBI):** Latent TB Infection; **(IGRA):** Interferon-Gamma Release Assay; **(TST):** Tuberculin Skin Test; **(LLOD):** Lower Limit of Detection; **(CI):** confidence interval; **(HSD):** Honest Significant Difference**; (SES):** socioeconomic status; **(M.tb):** Mycobacterium tuberculosis; **(INER):** Instituto Nacional de Enfermedades Respiratorias; **(AGEs):** advanced glycation end products; **(PAMPS):** Pathogen-Associated Molecular Patterns; **(HDT)** host-directed therapies; **(ADT):** Antituberculosis Therapy;

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