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Pulmonary Tuberculosis and Diabetes Comorbidity is Associated with Heightened Systemic Th1, Th17, Treg Cytokines and Others Biochemical Parameters

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Abstract

Background: This study aims to evaluate the impact of type 2 diabetes on pulmonary tuberculosis immune response. Methods: The tuberculosis diagnosis was based on the sputum smear and positivity of culture, whereas type 2 diabetes was diagnosis based on fasting blood sugar, 2-h PG, and glycated haemoglobin. Standardized techniques were used to obtain liver enzymes and lipid profiles whereas ELISA cytokine assay system was used to measured plasma cytokines levels. Results: fasting blood glucose ($p<0.0001$), 2hPG ($p = 0.0097$) and Glycated haemoglobin percentage ($p <0.0001$) in TB patients with diabetes were found to be significantly high as compare with TB patients without diabetes. While total cholesterol ($p= 0.0093$), serum triglycerides ($p= 0.0001$) and low-density lipoprotein cholesterol ($p= 0.0086$), were significantly high among Tb with diabetes, whereas High density lipoprotein cholesterol found to be significantly ($p = 0.0002$) elevated among TB patients without diabetes. TB and diabetes linked with increase concentration of Th1 (IFN-γ and TNF-α), Th17 (IL-17A) and Treg cytokines. The systemic levels of analysed cytokines show a positive increase associated with the HbA1c levels among TB patients except with IL-6 where there was no association with glycated haemoglobin. A significantly increased association was found between IL-22 and IFN-γ plasmatic levels. Conclusion: Our study shows an increase in characterized TB diabetics patients in cytokine response, signalizing that type 2 diabetes potentially participate in chronic inflammation that increases pathology and low control of tuberculosis.

Pulmonary Tuberculosis and Diabetes Comorbidity is Associated with Heightened Systemic Th1, Th17, Treg Cytokines and Others Biochemical Parameters

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Keys words , Tuberculosis, cytokines, type 2 diabetes

Abbreviation: interferon-γ (IFN-γ), interleukin (IL), Tumor necrosis factor-α (TNF-α), Type 1 (Th1); Regulatory T-cells (Treg), Type 17 (Th17), 2hours plasma glucose (2hPG), American Diabetes Association (ADA), pulmonary tuberculosis (TB), glycated hemoglobin (HbA1c), Tuberculosis with diabetes mellitus (TB–DM); Tuberculosis without diabetes mellitus (TB–NDM), Random blood sugar (RBS), Cameroon Bioethics Initiative (CAMBIN), natural killer (NK), natural killer T (NKT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma glutamyltransferase (δGT) and Alanine aminotransferase (ALP)

ABSTRACT

Background: This study aims to evaluate the impact of type 2 diabetes on pulmonary tuberculosis immune response. **Methods:**The tuberculosis diagnosis was based on the sputum smear and positivity of culture, whereas type 2 diabetes was diagnosis based on fasting blood sugar, 2-h PG, and glycated haemoglobin. Standardized techniques were used to obtain liver enzymes and lipid profiles whereas ELISA cytokine assay system was used to measured plasma cytokines levels.**Results:** fasting blood glucose ($p<0.0001$), 2hPG ($p = 0.0097$) and Glycated haemoglobin percentage ($p <0.0001$) in TB patients with diabetes were found to be significantly high as compare with TB patients without diabetes. While total cholesterol ($p= 0.0093$), serum triglycerides ($p= 0.0001$) and low-density lipoprotein cholesterol ($p= 0.0086$), were significantly high among Tb with diabetes, whereas High density lipoprotein cholesterol found to be significantly ($p = 0.0002$) elevated among TB patients without diabetes. TB and diabetes linked with increase concentration of Th1 (IFN-γ and TNF-α), Th17 (IL-17A) and Treg cytokines. The systemic levels of analysed cytokines show a positive increase associated with the HbA1c levels among TB patients except with IL-6 where there was no association with glycated haemoglobin. A significantly increased association was found between IL-22 and IFN-γ plasmatic levels. **Conclusion:** Our study shows an increase in characterized TB diabetics patients in cytokine response, signalizing that type 2 diabetes potentially participate in chronic inflammation that increases pathology and low control of tuberculosis.

INTRODUCTION

Despite the improvement in tuberculosis (TB) therapy, the disease remains responsible for 2-3 million deaths annually worldwide. Its association with type 2 diabetes mellites is evident and has been recognized for centuries. It has been proven that, diabetes mellites is a leding cause of tuberculosis and it can felt the paqpect and medication outcome of the disease [1]. Several authors show the relative risk of diabetic patients to develop tuberculosis range from 2.44 to 8.33 compared to patients without diabetes [1, 2]. According to Dooley and Chaisson [1], as well as to Jeon and Murray [2], the possibility of developing tuberculosis among type 2 diabetes patients has been recognized through clinical and epidemiological studies [2]. It have been proove that type 2 diabetes is linked with the harshness of tuberculosis dpathology, touching at the same time the disease manifestations and the response to medication [1]. After all the clinical and epidemiological consequences of tuberculosis and diabetes, little data are available on the biochemical and immunological mechanisms of the susceptibility of TB to diabetes. The susceptibility of diabetes patients to tuberculosis

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has been attributed to factors among which macrophage and lymphocyte function as well as hyperglycaemia and insulin resistance [3, 4]. Previous studies in patients having both diabetes tuberculosis have shown a reduction of proinflammatory cytokines [5, 6]. A study conducted by Kumar and collaborators in children suffering from tuberculosis reported a suppressed level of T helper type 1 (Th1), Treg, and type 17 (Th17) cytokine in active tuberculosis [7]. Kumar et al. [8] also reported in pulmonary tuberculosis associated with prediabetic patients a dysregulated cytokine response. Another study conducted by Kumar et al.[3] on diabetic and non-diabetic patients with tuberculosis, it was reported heightening systemic Th1, Th17, and other proinflammatory cytokines. The immune response orchestrated by the immune systems to tuberculosis infection, with Th1, Treg and Th17 cytokines family have been proved to be involved in protection against tuberculosis disease [2], whereas Treg and anti-inflammatory cytokinesa and type 1 IFNs have proved to be linked with elevated susceptibility to disease [8]. This study aimed to evaluate the impact of type 2 diabetes on pulmonary TB. To achieve this, we assessed the plasma concentration of Th1, Treg and Th17 cytokines among patients suffering simultaneously from tuberculosis and diabetes and compare them with those of patients suffering from pulmonary tuberculosis without diabetes.

2. METHODS

2.1. STUDY POPULATION

Our study was based on a group of 42 active pulmonary tuberculosis (TB) patients newly diagnosed at the Tuberculosis Reference Laboratory Bamenda North West Region of Cameroon. Among the 42 patients recruited in this study, 21 had diabetes and the other 21 without. The diagnosis of tuberculosis was through the sputum smear and positivity of the culture. The diagnosis of type 2 was done from American Diabetes Association [ADA] guidelines of fasting blood sugar [?] 126 mg/dl or 2-hours plasma glucose (PG) [?] 200 mg/dl but also glycated haemoglobin (HbA1c) cut-off point 6.5%. Fasting blood glucose was performed on capillary blood after overnight fasting (at least 10 hours without eating or smoking but can drink water during this period)[9]. Random blood sugar (RBS) level was measured using the OneTouch Ultra W glucometer from Johnson and Johnson Company, United Kingdom [9].. The 2h-PG was performed by giving 75 g anhydrous glucose dissolved in 200-300 ml of water to patients to be consumed within 5 minutes, followed by a further 100 ml of water; and capillary plasma glucose was measured after 2 hours [9]. Only those with apparently normal (fasting blood glucose level less than 99 mg/dL) glucose levels were subjected to the oral glucose tolerance test and patients were considered diabetic if two successive weeks' measurement of fasting blood glucose [?] 126 mg/dl or 2h-plasma glucose [?] 200 mg/dl [9]. In a patient with classic symptoms of hyperglycaemia tor hyperglycaemic crisis, only random plasma glucose and HbA1c were performed and the patient was considered diabetic if two successive weeks random plasma glucose [?] 200 mg/dl and HbA1c [?] 6.5% [9]. All the participants were HIV negative, were newly diagnosed and not under anti-tuberculosis treatment. No significant difference was observed in the two groups regarding the smear grades, thought the TB diabetes group presented a slightly high smear grade. Anthropometric parameters, among wihich, height, weight, and waist circumference; and biochemical parameters including blood glucose level, lipid profile and liver enzymes were obtained by standardized techniques as detailed by the International Federation of Clinical Chemistry and Laboratory Medicine [10]

2.2 DETERMINATION OF CIRCULATING CYTOKINES LEVELS

The concentration of plasma cytokines was determine using a ELISA cytokine assay system (Sino Biological Inc). Analysed parameters include IFN-γ, Tumor necrosis factor (TNF)-α, IL-1β, IL-12, IL-4, IL-6, IL-10, IL-17A and IL-22.

2.3 STATISTICAL ANALYSIS

Continuous variables from subjects' characteristics and cytokines plasma concentration were express as means ($\pm$ Standard Deviation) for parametric data and medians (Inter Quartile Ranges, IQR) for non-parametric data. Comparison between diabetic and non-diabetic sets of TB positive subjects was made using the t-test and non-parametric Mann-Whitney U test as appropriate for continuous variables, then correlations between glycated haemoglobin (Hb1Ac) and cytokines levels were done using Spearman "r" value. The level

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of statistical significance was set at $p < 0.05$. Statistical analysis was performed using GraphPad version 8.0.2 Software, San Diego, California, USA.

2.4 ETHICAL CONSIDERATION

The ethical clearance was obtained from ≪Ethics Review and Consultancy Committee of Cameroon Bioethics Initiative (CAMBIN)≫ (CBI/294/ERCC/CAMBIN) and informed written and signed consent was obtained from each participant.

3. RESULTS

3.1 CHARACTERISTICS OF THE STUDY POPULATION

The characteristics of the study population include anthropometric, clinical and biochemical features are presented in Table 1 compared with patients with and those without diabetes. No significant difference was observed in anthropometric (Age (year)), Sex, M/F, BMI, kg/m2 and Waist circumference) between TB patients with and without diabetes. Clinical parameters were found to be significantly high in TB with diabetes [fasting blood glucose ($p<0.0001$), 2hPG ($p = 0.0097$) and glycated haemoglobin % ($p <0.0001$)] compared to TB patients without diabetes. While with biochemical features, Total cholesterol ($p= 0.0093$), Serum triglycerides ($p= 0.0001$) and Low-density lipoprotein cholesterol ($p= 0.0086$), were significantly high among TB with diabetes, whereas High-density lipoprotein cholesterol found to be significantly ($p = 0.0002$) high among TB patients without diabetes. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyltransferase (δGT) and Alanine aminotransferase (ALP) shows no significant differences between the two study populations.

3.2 IMPACT OF DIABETES ON THE SERUM CIRCULATING LEVEL OF TYPE 1, TREG AND TYPE 17 CYTOKINE

To evaluate the impact of type 2 diabetes on Th1, Treg and Th17 cytokines on tuberculosis, we determine the plasma concentration of interferon-gamma (IFN-γ), Tumor necrosis factor (TNF)- α, interleukin (IL) namely: IL-1β, IL-12, IL-4, IL-6, IL-10, IL-17A and IL-22 in TB patients with and without diabetes (Figure 1). Figure 1, shows the geometric mean of circulating concentration of Th1 cytokines, namely IFN-γ (794.5 ± 326.2 pg/ml vs. 147.8 ± 130.5 pg/ml) and TNF-α (800.9 ± 372.7 pg/ml vs 500.6 ± 324,9 pg/ml) to be highly important among diabetics compared to patients without diabetes. The plasma concentration of Treg cytokine IL-10 (160.7± 81.03 pg/ml vs 68.2 ± 67.72 pg/ml) also found to highly increased in patients with diabetes compared to those without. Furthermore, the plasma concentration of Th17cytokine IL-17A was found to be also significantly high among diabetes compared to non-diabetic patients with tuberculosis (229.0 +- 187.4 pg/ml vs 105.7 +- 108,4 pg/ml). Contrary, IL-22 (7.09 +- 3.538 pg/ml vs 22.720 +- 2.278 pg/ml) was found to be present at significantly lower concentration in patients with diabetes compared to those without. Thus, active pulmonary tuberculosis patients with diabetes are associated with high plasma concentration of IFN-γ and TNF-α, Th17, IL-17A and Treg cytokines.

3.3 CORRELATION BETWEEN PLASMA CYTOKINES AND HBA1C CONCENTRATION

HbA1c is an accurate indicator of the level of diabetic control and high values reflect poor control of blood glucose level [11]. To evaluate the relationship between the plasma concentration of Th1, Th17 and Treg cytokines, with the level of diabetic complication, we determine the link of IFN-γ, TNF-α, IL-6, IL-10, IL-17A, and IL-22 with HbA1c concentration in all the individuals in the study. As presented in Figure 2, the plasma concentration of IFN-γ, TNF-α, IL-10, IL-17A, and IL-22 and IL-10 each shows an important positive association with the HbA1c concentration among TB patients. This was not the case with IL-6 where there was not associated with glycated haemoglobin.

3.4 INˆPREASEDˆ OPPELATION OΦ INΦ-γ ANˆD IΛ-22 AMONG ˆDIABETIˆ PATIENTˆS ΩITH INAˆTI˝E PYΛMONARΨ TYBERˆYΛOˆSIˆS

In the goal of discriminating Diabetic from non-diabetic TB positive individuals, the correlation between pro- and anti-inflammatory cytokines plasmatic levels was determined as shown in Figure 3. These data showed

a significantly increased association between IL-22 and IFN-γ plasmatic levels (r=0.5150; p=0.0005).

4. DISCUSSION

The immune components are altered in type 2 diabetes mellitus. Changes include specific cytokines, the activation process and state of immune cell subsets, as well as an increase of tissue apoptosis and fibrosis [12]. This may be since inflammation involve in the type 2 diabetes pathogenesis, but also how these affect the response to antigens remains unclear. It has been proved a diabetic patient are almost 3 times more likely to develop tuberculosis than a non-diabetic. The immunological basis for this susceptibility is not yet well understood. One possible explanation is dysglycaemia in which both diabetic and prediabetic impairs immune function and, in consequence, permits the primary infection or the reactivation of latent TB [13, 14]. According to Kumar and Babu (2017), immune responses against microbial pathogens in patients with diabetes are compromised, particularly in patients with chronic hyperglycemia [12]. The application of this to tuberculosis infection is not well-documented [15]. The infection outcome of host defence against mycobacterial infections is mediated mostly by cytokines among which IFN-γ and TNF-α are of major importance for host defence against intracellular infection by activating cellular immunity to kill bacterial and infected cells [15, 16].

Newly recognized Th17 cells have provided new observation on important mechanisms in antimicrobial host defence including M. tuberculosis [17, 18], though the exact role of IL-17 in the Mycobacterium tuberculosis infection is still unclear. Our results on concomitant tuberculosis and diabetes patients show an important type of cytokine expression. Firstly, the expression of cytokines implicated in the protection against infection, namely IFN-γ, TNF-α, IL-6, IL-10 and IL-17A, are all expressed at higher concentration in diabetics inpatients. Secondly, those not having a role in resistance, including IL-22, are present at much lower levels. The activation of Th17 cells results in a large production of inflammatory cytokines including 17A (IL-17A)/IL-17F, IL-21, IL-22 and IL-23, which are produced by Th17/Th22 cells or involved in their development(16) 17 and can also be produced by CD4+ T, CD8+ T, γδ T, natural killer T (NKT) and NK cell(19). IL-17A plays a critical role in preventing MTB infection through the induction of mature granuloma formation [19, 20]. IL-22 stimulates the secretion of antibacterial peptides, including β-defensins, lipocalin and islet-3-γ regenerating from lung epithelial cells and monocytes and macrophages to destroy pathogens. In addition to this, IL-22 can activate macrophages to mediate mycobacterial control and induce TNF-α production [21]. Our study, therefore, suggests that in TB diabetes patients, the regulation of IL-17A is different compared to IL-22. However, cell-mediated immune responses are distorted in patients having resistance to insulin, which may point out T-cell factors are associated with insulin sensitivity imbalance. Surely, T cells having CD4+ markers also known as T cells CD4+ that produce IL-17A and IFN-γ rise in magnitude and frequency and promote inflammation and produce several cytokines through Th1 or Th17 cells linked on resistance to insulin [22]. Moreover, type 2 diabetes has also been proven to lower natural regulatory T cells frequencies, demonstrating the imbalance of proinflammatory cytokines in type 2 diabetes patients [23]. Therefore, underlying needy diabetes controlled by itself could lead to an increase in Th1, Th2 and Th17 cytokines observed in TB diabetic patients. The increased production of Th1, Th2 and Th17 cytokines is linked with important plasma concentration of interleukin-1 family and other cytokines having proinflammatory activities. The pro-inflammatory cytokines IL-1α, IL-1β and IL-18, are members of the IL-1 family. IL-1α is important for resistance to infection, whereas, IL-12 also showed to produce a protective action against Mycobacterium tuberculosis [24]. Interleukin-6 (IL-6) is a pleiotropic cytokine produced in response to inflammatory stimuli and is involved in the essential cellular processes of differentiation, proliferation, and apoptosis [24]. It has been proven to intermediate in the inhibition of disease advancement [25]. The possible well work for the rise in baseline concentration of proinflammatory cytokines in patients with tuberculosis diabetes commodity could be both a decrease in the levels of plasma cytokines regulatory as shown by the decrease of plasma concentration of IL-4 and IL-10. Elsewhere, regulation of Treg cytokines are known to play a role in increasing touchiness to infection. Nevertheless, this study suggests that host protective cytokines do not expose to altered homeostasis production but are currently present in high concentrations in patients with tuberculosis and diabetes and are not linked to a decrease in the production of host protective cytokines proinflammatory.

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CONCLUSION

The baseline characteristics of anthropometric shows no significant difference between TB with diabetes and without diabetes. Clinical parameters were found to be significantly high in TB with diabetes compared to TB without diabetes, while some with biochemical features except for high-density lipoprotein cholesterol found to be significantly high among TB patients without diabetes, others found to be significantly high among TB patients with diabetes. Pulmonary TB with diabetes is linked with a high concentration of Th1 (IFN-γ and TNF-α), Th17 (IL-17A) and Treg cytokines. The plasma concentration of IFN-γ, TNF-α, IL-10, IL-17A, and IL-22 and IL-10 exhibited each an important positive association with the HbA1c concentration in the TB patients except with IL-6 where there is no association with glycated haemoglobin. A significantly increased association was found between IL-22 and IFN-γ plasmatic levels.

Declaration

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Disclosure

The authors declare that they have no competing interests.

Author's contributions

LFS and CBT designed the study. LSF and OK performed the field data collection, TFT and OBN analyzed the data, LSF, IMA, STB wrote the manuscript; all the authors read and approved the final manuscript.

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Data availability statement

No additional data that support this finding of this study is available.

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Table 1. Anthropometric and biochemical parameters of TB-DM and TB without DM

Charactéristics	TB–DM	TB–NDM	P-value
	(n = 21)	(n = 21)	
Age (year)	46.76±2.789	46.95±2.816)	0.9619
Sex, M/F	10/11	11/10	0.9999
BMI, kg/m2	19.81±0.9611	20.19±1.027	0.7882
Waist circumference	79.29±2.014	80.29±2.240	0.7417
Fasting blood glucose (mg/dl)	10.52±0.9521	5.70±0.1721	<0.0001
2h-PG (mg /dl)	11.30±1.815	6.88±0.3133	0.0097
HbA1c (%)	12.42±1.678	4.265±2.221	<0.0001
Total cholesterol (mg/dl)	157 (132–198)	131 (109–198)	0.0093
Serum triglycerides (mg/dl)	143 (56–398)	48 (26–317)	0.0001
HDL cholesterol (mg/dl)	39 (32–63)	49 (28–70)	0.0002
LDL cholesterol (mgdl)	109 (51–162)	92 (42–136)	0.0086
ASAT (U/l)	247.6 (7.2-73,5)	239.8 (3.3-30.4)	0.8813
ALAT (U/l)	379.8 (43.8-486,9)	325.5 (108.1-633,5)	0.5499
γ-GT (U/l)	379.8 (43.8-486,9)	325.5 (108.1-633.5)	0.8178
ALP (U/l)	64.79 (221.8-616)	31.71 (177.2-691.3)	0.2403

2h-PG = 2hours plasma glucose; ALP = Alkaline phosphatase; ALAT = Alanine aminotransferase; ASAT = Aspartate aminotransferase; BMI = Body mass index; γ-GT = Gamma glutamyl transferase; M/F = male/female; HbA1c = Glycated hemoglobin; HDL = High density lipoprotein; LDL = Low density lipoprotein; OGTT = Oral glucose tolerant test; TB–DM = Tuberculosis with diabetes mellitus; TB–NDM =

Tuberculosis without diabetes mellitus.

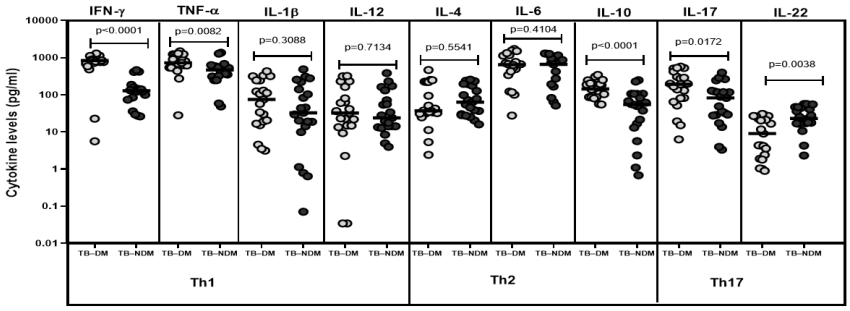

Figure 1. Circulating levels of T helper type 1, Treg and type 17 cytokines.

TB–DM = Tuberculosis with diabetes mellitus; TB–NDM = Tuberculosis without diabetes mellitus. IFN-γ = Interferon gamma; TNF-α = Tumor Necrosis factor alpha; Ilβ =Interleukine-1 Beta; IL12 = Interleukine-12; IL4 = Interleukine-4; IL6 = Interleukine-6; IL10 = Interleukine-10; IL17 = Interleukine-17; IL22 = Interleukine-22; Th1 = Type 1 helper T-cells; Treg = regulatory T-cells; Th17 = Type 17 helper T-cells

Figure 2 . Correlation between plasma concentration of cytokines and glycated hemoglobin (HbA1c) concentrations in TB patients.

Figure 3 . The supply of IFN-γ and IL-22 on the discrimination TB diabetics to TB non diabetics patients

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