Summer 8-7-2018

Latent Tuberculosis Infection and Dyslipidemia among Refugees Attending a Community Based Clinic in Georgia

Dolgion Erdenebat

ABSTRACT

LATENT TUBERCULOSIS INFECTION AND DYSLIPDEMIA AMONG REFUGEES ATTENDING A COMMUNITY BASED CLINIC IN GEORGIA

By

DOLGION ERDENEBAT

JULY 23, 2018

Background: Emerging epidemiologic evidence indicates tuberculosis (TB) disease may increase the risk of non-communicable disease, including cardiovascular diseases (CVD). However, limited data exists on the association between latent TB infection (LTBI) and dyslipidemia, a key precursor to CVD.

Objective: To determine the association between LTBI and dyslipidemia among newly arrived refugees to the US.

Methods: We conducted a cross-sectional study among new refugees who received care at the DeKalb County Board of Health Refugee Clinic, Atlanta, Georgia between 1st October 2013 and 31st August 2014. Eligible participants included adult refugees (age ≥21 years) who had valid QuantiFERON-TB Gold In-Tube (QFT) and blood lipid test results. Participants with a history of TB disease were excluded. QFT was used to define LTBI and dyslipidemia was defined by three blood lipid levels: total cholesterol, high-density lipoproteins (HDL), and triglycerides (TGL).

Results: Among eligible participants (n=684), the prevalence of LTBI was 31.9%. Overall 30.6% (209/684) had elevated total cholesterol, 44% (301/684) had low HDL-C, and 40.7% (276/684) had elevated TGL. Participants with LTBI had a similar prevalence of elevated total cholesterol (35.3% vs 28.3%, p-value=0.06) and elevated triglycerides (44.5% vs 38.4%, p-value=0.13) compared to participants without LTBI. Low HDL-C was also similar in participants with and without LTBI (45.7 vs 40.4%, p-value=0.64). After adjusting for age, sex, body mass index and diabetes mellitus, LTBI was non-significantly associated with elevated total cholesterol (adjusted odds ratio [aOR] 1.27; 95%CI 0.89-1.82) and elevated triglycerides (aOR 1.18; 95% CI 0.84-1.67).

Conclusion: Among recently arrived refugees in the US, we did not observe a statistically significant association between LTBI and dyslipidemia. Additional research is needed to determine mechanisms that may increase the risk of non-communicable disease in patients with TB disease and infection.

LATENT TUBERCULOSIS INFECTION AND DYSLIPDEMIA AMONG REFUGEES ATTENDING A COMMUNITY BASED CLINIC IN GEORGIA

by

DOLGION ERDENEBAT

BMedSci., MONGOLIAN NATIONAL UNIVERSITY OF MEDICAL SCIENCE

A Thesis Submitted to the Graduate Faculty

of Georgia State University in Partial Fulfillment

of the

Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

30303

APPROVAL PAGE

LATENT TUBERCULOSIS INFECTION AND DYSLIPDEMIA AMONG REFUGEES ATTENDING A COMMUNITY BASED CLINIC IN GEORGIA

by

DOLGION ERDENEBAT

Approved:

Matthew J.Magee, PhD, MPH

Committee Chair

Unjali Gujral, PhD, MPH

Committee Member

July 18, 2018

Date

ACKNOWLEDGMENTS

First, I would like to thank my family, for their love and support.

Secondly, I would like to express my sincere gratitude to my committee chair Professor Matthew Magee for his valuable support and effort towards my thesis and study. I learned a lot, grew as an epidemiologist, and managed to complete my thesis successfully thanks to his mentorship.

I would also like to thank Dr. Unjali Gujral, my committee member for her time dedication and feedback on this work.

Last but not least, I would like to thank the Fulbright Program for providing me an opportunity to complete my master's program at Georgia State University. I shall forever treasure this episode as a memorable and wonderful journey of my life.

Author's Statement Page

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this thesis may be granted by the author or, in his/her absence, by the professor under whose direction it was written, or in his/her absence, by the Associate Dean, School of Public Health. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve potential financial gain. It is understood that any copying from or publication of this dissertation which involves potential financial gain will not be allowed without written permission of the author.

Dolgion Erdenebat

Signature of Author

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium Tuberculosis* (MTB) that mainly affects the lungs (WHO, 2017). Globally, TB is a leading public health problem causing high morbidity and mortality, particularly in low and middle-income countries (WHO, 2017). The World Health Organization (WHO) estimated that 10.4 million new TB cases occurred in 2016, affecting 6.2 million men, 3.2 million women and 1 million children. In 2016 TB was the ninth leading cause of death in the world, causing 1.7 million deaths (WHO, 2017). An estimated 1.7 billion people, one-quarter of world's population, have latent TB infection (LTBI) which is an asymptomatic state consisting of MTB infection without bacteria activation (Houben & Dodd, 2016). Simultaneously, the global burden of cardiovascular disease (CVD) is steadily increasing and it is estimated that 422.7 million people have CVD and 1.7 million attributable deaths occur annually (Roth et al., 2017).

In recent years, studies indicate the association between TB and non-communicable disease, particularly cardiovascular diseases (Huaman, Henson, Ticona, Sterling, & Garvy, 2015). Studies reported that TB increases the risk of acute myocardial infarction (AMI) (Huaman et al., 2017), ischemic stroke (Sheu, Chiou, Kang, Chen, & Lin, 2010), and peripheral artery disease (Wang et al., 2017). Moreover, LTBI is associated with increased risk diabetes mellitus (DM) (Hensel et al., 2016) and identified as independent risk factor of AMI (Huaman et al., 2018). There are several potential mechanisms which may explain how TB contributes to the CVD. First, MTB may affect the coronary artery and myocardium directly (Huaman et al., 2015).

Second, chronic inflammation during active TB replication and granuloma formation could cause impairment of endothelial, leading to atherosclerosis just as other chronic inflammation (Huaman et al., 2015). Last, TB infection may interrupt the lipid metabolism. Lipid abnormalities are the main risk factor of the CVD, increasing the risk by the 1.5-2 times (Ahmed et al., 2016; Orozco-Beltran et al., 2017). Chronic inflammation, mediated by pro-inflammatory cytokines also has a potential effect on lipid metabolism (Elmehdawi, 2008). Low cholesterol was observed in patients with rheumatoid disorders and chronic bowl inflammatory disease (Elmehdawi, 2008). Similarly, patients with active TB had lower serum cholesterol comparing those without TB (Gebremicael et al., 2017). Cholesterol plays key role for replication, survival, dormancy, and reactivation of MTB (Brzostek, Pawelczyk, Rumijowska-Galewicz, Dziadek, & Dziadek, 2009; Rodriguez et al., 2014; Soto-Ramirez et al., 2017). MTB is capable of accumulating and utilizing cholesterol as an energy source and use it as protection from host immune-response and disrupt cholesterol metabolism at cellular level (Brzostek et al., 2009; Soto-Ramirez et al., 2017). Contrary, it is suggested that hypercholesterolemia could promote immunity impair towards TB infection and increase the TB susceptibility (Martens et al., 2008). However, whether lipid abnormalities support TB infection susceptibility or reverse relationship is not yet established.

In 2015, the estimated global prevalence of dyslipidemia (high cholesterol) was 39% (37% for males and 40% for females) and the highest in Region of Europe with 54%, followed by the Region of the Americas (48%), Western Pacific (36.7%) and Southeast Asia (30.3%) (Benjamin et al., 2017).

Given the high population prevalence of dyslipidemia as well as LTBI, an improved understanding of the relationship between TB infection and lipid abnormalities have the potential to greatly impact clinical treatment and prevention programs for TB and non-communicable diseases.

The objective of the study was to determine the association between LTBI and blood lipid abnormalities among newly arrived refugees to the US at a community clinic in Dekalb County, Georgia.

1.2 Gap and Purpose of Study

To date, few studies have assessed the association between LTBI and non-communicable diseases, particularly lipid abnormalities. Given the high prevalence of lipid abnormalities and its role in the pathogenesis of non-communicable disease, an improved understanding of the association between LTBI and dyslipidemia has the potential to improve clinical care and public health practice.

Our study addressed the association between LTBI prevalence and dyslipidemia, evaluating the the hypothesis that LTBI may increase the prevalence of dyslipidemia.

Therefore, we had following aims:

1. To determine the prevalence of dyslipidemia among newly arrived refugees at Dekalb County, Atlanta, Georgia.
2. To identify the cross-sectional association between LTBI and dyslipidemia.
3. To define the association between LTBI and severity (level) of dyslipidemia.

CHAPTER II

LITERATURE REVIEW

2.1 Burden of LTBI

LTBI is defined as "A state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB" (WHO, 2018). It is estimated that 25% of the population (1.7 billion people) are infected with MTB (Houben & Dodd, 2016). However, an estimated 10% of those with LTBI will develop TB disease in their lifetime, while rest of them contain the infection by developing granulomas. After 6-8 weeks of infection, due type IV hypersensitivity (delayed type hypersensitivity) to MTB, the granulomas undergo necrosis, causing death for most of the tuberculosis bacilli and leaving a small proportion of the bacilli surviving at the inactive stage and results in LTBI (Dutta & Karakousis, 2014). However, people with LTBI remain at risk of developing the active TB (lifetime risk 5-15%) and managing LTBI is the critical part for the reducing the high burden of TB (S. J. Lee et al., 2014). While the global prevalence was 23%, the highest prevalence observed in region of South East Asia with 30.8%, followed by Western Pacific region (27.9%); African region (22.4%) and the American region (11.0%) and European region (13.7%) had the lower prevalence (Houben & Dodd, 2016). From the country-specific studies 31% of the population of Ethiopia had LTBI, while it was 49% in Uganda, 55.2% in South Africa (Basera, Ncayiyana, & Engel, 2017), 20% in Eastern China (Chen et al., 2015); and 28.6% in South Korea (S. J. Lee et al., 2014) . In the US, it is estimated that 12.4-13.6 million people had LTBI and 73% of them are non-US born (Mancuso, Diffenderfer, Ghassemieh, Horne, & Kao, 2016). LTBI is common among populations such as mining workers, health care providers and prisoners.

The prevalence of LTBI among healthcare workers of high TB burden counties was 47%, with the lowest as 37% (Brazil) and the highest as 64% (South Africa) (Nasreen, Shokoohi, & Malvankar-Mehta, 2016). It was also documented high among miners with the prevalence of 89% (Hanifa et al., 2009), and 70.3% among prisoners in middle and high TB burden countries (70.3%) (Kawatsu, Uchimura, Izumi, & Ohkado, 2016).

2.2 Burden of Dyslipidemia

Dyslipidemia was defined as elevated cholesterol and triglycerides and lower high-density lipoproteins cholesterol (HDL-C) (American Association of Clinical Endocrinologists and American College of Endocrinology, 2017). Because it is the main risk factor of CVD, the dyslipidemia has become the public health problem (Najafipour et al., 2016). The low HDL increased the coronary heart disease risk (CHD) (adjusted risk ratio [aRR] 1.31, 95% confidence interval [CI] 1.18-1.45) among adults who are 30 years old and older in study from Spain (Orozco-Beltran et al., 2017) and CVD risk by almost 2-fold (aHR 1.93, 95% CI 1.11-3.34) among adults four ethnic-race groups in US (Abd Alamir et al., 2018). The MESA also showed that hypercholesterolemia and lower HDL were significantly associated with higher Agatston CAC score (Abd Alamir et al., 2018). The adjusted prevalence ratio of elevated cholesterol and lower HDL was 1.55 (95% CI 1.26-1.92) and 1.2 (1.02-1.40) (Abd Alamir et al., 2018). The US study used Kaiser Permanente Southern California (KPSC) healthcare system found that elevated LDL and TGL increased the risk of CHD among US adults, while high HDL had protective effect with the hazard ratio of 1.49 (95% CI 1.38-1.61), 1.75 (95% CI 1.61-1.90) and 0.55 (95% CI 0.50-0.60) (Colantonio et al., 2016).

The prevalence of dyslipidemia is high globally, the estimated global prevalence was 39% (37% for males and 40% for females) and the highest in Region of Europe with 54%, followed by the Region of the Americas (48%), Western Pacific (36.7%) and Southeast Asia (30.3%) (Benjamin et al., 2017). The several studies indicated a high prevalence of dyslipidemia. The recent study in South Korea, the prevalence of dyslipidemia was 39.6% (J. Lee, Son, & Ryu, 2017) and similar result in China with 35.5% for dyslipidemia, 44.2% for hypertriglyceridemia and 14.7% for hypercholesterolemia (Qi et al., 2015) and Thailand with the prevalence of 29.6% for elevated LDL, 47.1% for lower HDL and 38.6% for hypertriglyceridemia (Aekplakorn et al., 2014).

2.3 The association between LTBI and dyslipidemia

The evidence on LTBI relating to dyslipidemia is scarce. However, the association between the TB and non-communicable disease, particularly the cardiovascular disease is documented in recent years. The study in the US indicated that pulmonary tuberculosis increased the risk of AMI by almost 3 times (aHR 2·43, 95% CI 1·5–4·1) (Huaman et al., 2017) and from another population-based study in Taiwan, 40% increased acute coronary syndrome among TB patients (Chung et al., 2014). Besides, recent studies suggest the possible association between LTBI and CVD and metabolic disorder (Huaman et al., 2015; Huaman et al., 2018). The people with LTBI had 1.9 times more odds having AMI (Huaman et al., 2018) and patients with DM were likely to have LTBI (aOR 2.3, CI 95% CI 1.2-4.5) compared to those without DM (Hensel et al., 2016).

Various mechanisms potentially involved in TB and CVD association. Chronic inflammation, elevated pro-inflammatory cytokines caused by the TB granuloma formation could affect the coronary artery (tuberculosis arteritis) and myocardium (tuberculosis myocarditis) directly. Also could cause endothelial damage and subsequently the atherosclerosis (Huaman et al., 2015). In addition, TB infection could also be associated with lipid abnormalities, which are a primary risk

factor for CVD. The chronic inflammation, pro-inflammatory cytokines are known for association with lipid abnormalities (Elmehdawi, 2008). The patients with chronic inflammation disorder such as rheumatoid disorders and chronic bowl inflammatory disease tend to have lower cholesterol (Elmehdawi, 2008). Similar to other chronic inflammatory diseases, patients with active TB had lower cholesterol comparing those without TB (Gebremicael et al., 2017). On the other hand, hypercholesterolemia could delay the immune activity towards MTB infection and increase the risk of TB susceptibility (Martens et al., 2008). And at the cellular level cholesterol plays important role for MTB replication, survival, dormancy, and reactivation of MTB. MTB is capable of accumulating and utilizing cholesterol as important energy source and use it as protection from host immune-response and disrupt cellular cholesterol metabolism (Brzostek et al., 2009). However, whether lipid abnormalities support TB infection susceptibility or reverse relationship is not yet established.

2.4 Summary of literature review

Highlights from the literature review:

- LTBI prevalence globally is high, especially in low and middle-income countries and high-risk populations such as miners, health care workers and prisoners.
- LTBI might have possible contribution to the non-communicable diseases, in particular to DM and CVD
- Many non-communicable diseases are risk factors for TB disease, reactivation of LTBI and poor TB outcome. However, recent evidences suggest the potential reverse association: that TB disease and LTBI may increase the risk of non-communicable diseases, particularly CVD.
- There is a possibility that LTBI might play a role in lipid abnormalities which is a primary risk factor for CVD. The relationship between LTBI and dyslipidemia is under studied.

REFERENCES

Abd Alamir, M., Goyfman, M., Chaus, A., Dabbous, F., Tamura, L., Sandfort, V., . . . Budoff, M. (2018). The Correlation of Dyslipidemia with the Extent of Coronary Artery Disease in the Multiethnic Study of Atherosclerosis. *J Lipids, 2018*, 5607349. doi:10.1155/2018/5607349

Aekplakorn, W., Taneepanichskul, S., Kessomboon, P., Chongsuvivatwong, V., Putwatana, P., Sritara, P., . . . Chariyalertsak, S. (2014). Prevalence of Dyslipidemia and Management in the Thai Population, National Health Examination Survey IV, 2009. *J Lipids, 2014*, 249584. doi:10.1155/2014/249584

Ahmed, H. M., Miller, M., Nasir, K., McEvoy, J. W., Herrington, D., Blumenthal, R. S., & Blaha, M. J. (2016). Primary Low Level of High-Density Lipoprotein Cholesterol and Risks of Coronary Heart Disease, Cardiovascular Disease, and Death: Results From the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol, 183*(10), 875-883. doi:10.1093/aje/kwv305

American Association of Clinical Endocrinologists and American College of Endocrinology. (2017). American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease 2017. Retrieved from https://www.aace.com/files/lipid-guidelines.pdf

Basera, T. J., Ncayiyana, J., & Engel, M. E. (2017). Prevalence and risk factors of latent tuberculosis infection in Africa: a systematic review and meta-analysis protocol. *BMJ Open, 7*(7), e012636. doi:10.1136/bmjopen-2016-012636

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., . . . Stroke Statistics, S. (2017). Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation, 135*(10), e146-e603. doi:10.1161/CIR.0000000000000485

Brzostek, A., Pawelczyk, J., Rumijowska-Galewicz, A., Dziadek, B., & Dziadek, J. (2009). Mycobacterium tuberculosis is able to accumulate and utilize cholesterol. *J Bacteriol, 191*(21), 6584-6591. doi:10.1128/JB.00488-09

Chen, C., Zhu, T., Wang, Z., Peng, H., Kong, W., Zhou, Y., . . . Lu, W. (2015). High Latent TB Infection Rate and Associated Risk Factors in the Eastern China of Low TB Incidence. *PLoS One, 10*(10), e0141511. doi:10.1371/journal.pone.0141511

Chung, W. S., Lin, C. L., Hung, C. T., Chu, Y. H., Sung, F. C., Kao, C. H., & Yeh, J. J. (2014). Tuberculosis increases the subsequent risk of acute coronary syndrome: a nationwide population-based cohort study. *Int J Tuberc Lung Dis, 18*(1), 79-83. doi:10.5588/ijtld.13.0288

Colantonio, L. D., Bittner, V., Reynolds, K., Levitan, E. B., Rosenson, R. S., Banach, M., . . . Muntner, P. (2016). Association of Serum Lipids and Coronary Heart Disease in Contemporary Observational Studies. *Circulation, 133*(3), 256-264. doi:10.1161/CIRCULATIONAHA.115.011646

Dutta, N. K., & Karakousis, P. C. (2014). Latent tuberculosis infection: myths, models, and molecular mechanisms. *Microbiol Mol Biol Rev, 78*(3), 343-371. doi:10.1128/MMBR.00010-14

Elmehdawi, R. (2008). Hypolipidemia: a word of caution. *Libyan J Med, 3*(2), 84-90. doi:10.4176/071221

Gebremicael, G., Amare, Y., Challa, F., Gebreegziabxier, A., Medhin, G., Wolde, M., & Kassa, D. (2017). Lipid Profile in Tuberculosis Patients with and without Human Immunodeficiency Virus Infection. *Int J Chronic Dis, 2017*, 3843291. doi:10.1155/2017/3843291

Hanifa, Y., Grant, A. D., Lewis, J., Corbett, E. L., Fielding, K., & Churchyard, G. (2009). Prevalence of latent tuberculosis infection among gold miners in South Africa. *Int J Tuberc Lung Dis, 13*(1), 39-46.

Hensel, R. L., Kempker, R. R., Tapia, J., Oladele, A., Blumberg, H. M., & Magee, M. J. (2016). Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus. *Int J Tuberc Lung Dis, 20*(1), 71-78. doi:10.5588/ijtld.15.0457

Houben, R. M., & Dodd, P. J. (2016). The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med, 13*(10), e1002152. doi:10.1371/journal.pmed.1002152

Huaman, M. A., Henson, D., Ticona, E., Sterling, T. R., & Garvy, B. A. (2015). Tuberculosis and Cardiovascular Disease: Linking the Epidemics. *Trop Dis Travel Med Vaccines, 1*. doi:10.1186/s40794-015-0014-5

Huaman, M. A., Kryscio, R. J., Fichtenbaum, C. J., Henson, D., Salt, E., Sterling, T. R., & Garvy, B. A. (2017). Tuberculosis and risk of acute myocardial infarction: a propensity score-matched analysis. *Epidemiol Infect, 145*(7), 1363-1367. doi:10.1017/S0950268817000279

Huaman, M. A., Ticona, E., Miranda, G., Kryscio, R. J., Mugruza, R., Aranda, E., . . . Garvy, B. A. (2018). The Relationship Between Latent Tuberculosis Infection and Acute Myocardial Infarction. *Clin Infect Dis, 66*(6), 886-892. doi:10.1093/cid/cix910

Kawatsu, L., Uchimura, K., Izumi, K., & Ohkado, A. (2016). [a Systematic Review on the Prevalence and Incidence of Latent Tuberculosis Infection among Prison Population]. *Kekkaku, 91*(4), 457-464.

Lee, J., Son, H., & Ryu, O. H. (2017). Management Status of Cardiovascular Disease Risk Factors for Dyslipidemia among Korean Adults. *Yonsei Med J, 58*(2), 326-338. doi:10.3349/ymj.2017.58.2.326

Lee, S. J., Lee, S. H., Kim, Y. E., Cho, Y. J., Jeong, Y. Y., Kim, H. C., . . . Menzies, D. (2014). Risk factors for latent tuberculosis infection in close contacts of active tuberculosis patients in South Korea: a prospective cohort study. *BMC Infect Dis, 14*, 566. doi:10.1186/s12879-014-0566-4

Mancuso, J. D., Diffenderfer, J. M., Ghassemieh, B. J., Horne, D. J., & Kao, T. C. (2016). The Prevalence of Latent Tuberculosis Infection in the United States. *Am J Respir Crit Care Med, 194*(4), 501-509. doi:10.1164/rccm.201508-1683OC

Martens, G. W., Arikan, M. C., Lee, J., Ren, F., Vallerskog, T., & Kornfeld, H. (2008). Hypercholesterolemia impairs immunity to tuberculosis. *Infect Immun, 76*(8), 3464-3472. doi:10.1128/IAI.00037-08

Najafipour, H., Shokoohi, M., Yousefzadeh, G., Sarvar Azimzadeh, B., Moshtaghi Kashanian, G., Bagheri, M. M., & Mirzazadeh, A. (2016). Prevalence of dyslipidemia and its association with other coronary artery disease risk factors among urban population in Southeast of Iran: results of the Kerman coronary artery disease risk factors study (KERCADRS). *J Diabetes Metab Disord, 15*, 49. doi:10.1186/s40200-016-0268-0

Nasreen, S., Shokoohi, M., & Malvankar-Mehta, M. S. (2016). Prevalence of Latent Tuberculosis among Health Care Workers in High Burden Countries: A Systematic Review and Meta-Analysis. *PLoS One, 11*(10), e0164034. doi:10.1371/journal.pone.0164034

Orozco-Beltran, D., Gil-Guillen, V. F., Redon, J., Martin-Moreno, J. M., Pallares-Carratala, V., Navarro-Perez, J., . . . Group, E. S. (2017). Lipid profile, cardiovascular disease and mortality in a Mediterranean high-risk population: The ESCARVAL-RISK study. *PLoS One, 12*(10), e0186196. doi:10.1371/journal.pone.0186196

Qi, L., Ding, X., Tang, W., Li, Q., Mao, D., & Wang, Y. (2015). Prevalence and Risk Factors Associated with Dyslipidemia in Chongqing, China. *Int J Environ Res Public Health, 12*(10), 13455-13465. doi:10.3390/ijerph121013455

Rodriguez, J. G., Hernandez, A. C., Helguera-Repetto, C., Aguilar Ayala, D., Guadarrama-Medina, R., Anzola, J. M., . . . Del Portillo, P. (2014). Global adaptation to a lipid environment triggers the dormancy-related phenotype of Mycobacterium tuberculosis. *MBio, 5*(3), e01125-01114. doi:10.1128/mBio.01125-14

Roth, G. A., Johnson, C., Abajobir, A., Abd-Allah, F., Abera, S. F., Abyu, G., . . . Murray, C. (2017). Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol, 70*(1), 1-25. doi:10.1016/j.jacc.2017.04.052

Sheu, J. J., Chiou, H. Y., Kang, J. H., Chen, Y. H., & Lin, H. C. (2010). Tuberculosis and the risk of ischemic stroke: a 3-year follow-up study. *Stroke, 41*(2), 244-249. doi:10.1161/STROKEAHA.109.567735

Soto-Ramirez, M. D., Aguilar-Ayala, D. A., Garcia-Morales, L., Rodriguez-Peredo, S. M., Badillo-Lopez, C., Rios-Muniz, D. E., . . . Gonzalez, Y. M. J. A. (2017). Cholesterol plays

a larger role during Mycobacterium tuberculosis in vitro dormancy and reactivation than previously suspected. *Tuberculosis (Edinb), 103*, 1-9. doi:10.1016/j.tube.2016.12.004

Wang, S. H., Chien, W. C., Chung, C. H., Lin, F. H., Peng, C. K., Chian, C. F., & Shen, C. H. (2017). Tuberculosis increases the risk of peripheral arterial disease: A nationwide population-based study. *Respirology, 22*(8), 1670-1676. doi:10.1111/resp.13117

WHO. (2017). Global TB Report 2017. Retrieved from http://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf

WHO. (2018). Latent TB infection: Updated and Consolidated guidelines for programmatic management, WHO 2018. Retrieved from http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/

CHAPTER III

MANUSCRIPT

INTRODUCTION

Tuberculosis (TB) remains an enormous public health problem, particularly in low-and middle-income countries, whereas 97% of the reported cases are reported [1]. It is estimated that 10.4 million new cases and 1.7 million deaths attributable to TB occurred in 2016 worldwide [1]. In addition, 25% of the world's population (1.7 billion people) are infected with Mycobacterium tuberculosis (MTB), resulting in a non-infectious and subclinical state called latent TB infection (LTBI) [2]. Those with LTBI are at risk of reactivation and subsequent progression to TB disease [3]. Simultaneously, the global burden of cardiovascular disease (CVD) is steadily increasing and it is estimated that 422.7 million people have CVD and 17 million attributable death occur annually [4].

Emerging evidence suggests that TB disease and TB infection may be associated with non-communicable diseases, in particular with CVD. The risk of acute myocardial infarction (AMI) [5] and ischemic stroke [6] and peripheral artery [7] disease was higher among TB patients. Additional evidence indicates that, LTBI is an independent risk factor of AMI [8]. TB disease or LTBI may contribute to CVD development by varying mechanisms. MTB could directly damage the myocardium (tuberculosis myocarditis) and coronary artery (tuberculosis arteritis) [9]. It is also possible that chronic immune activation towards MTB replication during the active TB disease may result in elevated production of pro-inflammatory cytokines which could lead to persistent inflammation and subsequent atherosclerosis [9]. Furthermore, TB infection could also be associated with lipid abnormalities, which are a primary risk factor for CVD development.

The chronic inflammation, pro-inflammatory cytokines are known for potential effect on lipid metabolism [10]. The low cholesterol was observed in patients with rheumatoid disorders and chronic bowl inflammatory disease [10]. Similarly, patients with active TB had lower serum cholesterol comparing those without TB [11]. Cholesterol plays key role for replication, survival, dormancy, and reactivation of MTB [12-14]. MTB is capable of accumulating and utilizing cholesterol as an energy source and use it as protection from host immune-response and disrupt cholesterol metabolism at cellular level [12, 13]. Contrary, it is suggested that hypercholesterolemia could promote immunity impair towards TB infection and increase the TB susceptibility [15].

However, whether lipid abnormalities support TB infection susceptibility or reverse relationship is not yet established.

Dyslipidemia increases the risk of CVD by almost 2 times [16, 17] and globally, 40% of the population has dyslipidemia [18]. Given the high population prevalence of dyslipidemia as well as LTBI, an improved understanding of the relationship between TB infection and lipid abnormalities has the potential to greatly impact clinical treatment and prevention programs for TB and non-communicable diseases. The objective of the study was to determine the association between LTBI and blood lipid abnormalities among newly arrived refugees to the US at a community clinic in Dekalb County, Georgia.

METHODS

Study design and participants

We conducted a cross-sectional study among refugees arriving to the US who received care at the DeKalb County Board of Health Refugee Clinic (Atlanta, Georgia, USA) between 1st October 2013 and 31st August 2014.

Refugees received a general health exam and screening as standard of care, which included measures of blood lipids (total cholesterol, low-density lipoproteins [LDL-C], high-density lipoproteins [HDL-C], and triglycerides [TGL]) and the QuantiFERON-TB Gold In-Tube (QFT) test for LTBI. Other medical information such as demographic characteristics, clinical history, and a general blood chemistry panel were also collected as part of standard practice. Eligible participants included all adults aged ≥ 21 years, who received refugee status from the US Department of State, had valid blood lipid tests (total cholesterol, HDL-C, and TGL) and QFT results available, and were treated at the DeKalb County clinic during the study period. Patients with TB disease were excluded.

Definitions

The study's primary exposure was LTBI defined by QFT test results. Patients were defined dichotomously as LTBI positive or negative according to manufacturer's instructions [19].

The primary outcome of the study was dyslipidemia, defined using three measures: 1) elevated total cholesterol (hypercholesterolemia), 2) low HDL-C, and 3) elevated TGL (hypertriglyceridemia). Any dyslipidemia was defined as presence of hypercholesterolemia or lower HDL-C or hypertriglyceridemia [20]. We defined dyslipidemia according to the American Association of Clinical Endocrinology Guidelines for Management of Dyslipidemia 2017 (AACE 2017) [21]; and Detection, Evaluation and Treatment of High Blood Cholesterol in Adults 2005 (Adult Panel Treatment III, ATP III) [20]. Elevated total cholesterol was defined as total serum cholesterol ≥ 200 mg/dl or greater (normal defined < 200 mg/dl) [21].

Low HDL-C was defined by serum HDL-C < 40 mg/dl in men and <50 mg/dl in women (normal defined 40 mg/dl or greater in men; 50 mg/dl or greater in women) [21]. Elevated TGL were defined by serum level ≥ 150mg/dl (normal defined <150mg/dl) [20] We also examined severity

of dyslipidemia using alternate classifications: Elevated total cholesterol was classified as "borderline high" with serum levels of 200-239 mg/dl and "high" ≥ 240 mg/dl; elevated TGL were classified as "borderline high" with serum levels of 150-199 mg/dl and "high" ≥ 200 mg/dl [20].

Covariates extracted from patient medical records included age, sex, current smoking status, country of origin, alcohol use, blood pressure, body mass index (BMI), and diabetes mellitus (DM) status. Additional laboratory results including hemoglobin, white blood cell count, random glucose, creatinine, glycated hemoglobin (HbA1c), vitamin D level, human immunodeficiency virus (HIV) serologic, hepatitis B (HbsAb and HBsAg), hepatitis C antibody, and syphilis infection were also extracted.

BMI was calculated as weight (kg)/height (m2). BMI was classified as underweight (<18.5 kg/m2), normal (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2) and obese (≥30.0 kg/m2) [22]. TB incidence of the country of origin (TB cases per 100000 population annually) was defined according to World Health Organization (WHO) Report [23]. Country TB incidence classification was defined as moderate (<100), medium (100-199) and high (≥300) by WHO classification [23].

DM status was defined based on glycated hemoglobin (HbA1c) ≥ 6.5% according to the American Diabetes Association Guideline 2017 [24] and/or a previous history of DM diagnosis. Participants were classified as having pre-DM if HbA1c was between 5.7% and 6.4% and no previous diagnosis of DM diagnosis.

We also assessed the association between LTBI and elevated LDL-C, combined dyslipidemia, and metabolic syndrome. Elevated LDL-C was defined as serum LDL-C ≥ 130 mg/dl. Combined dyslipidemia was defined as the presence of elevated LDL-C and hypertriglyceridemia.

An individual was categorized as having metabolic syndrome if they had all the following: high blood pressure (>140/90 mmHg), low HDL-C (less than 40 mg/dl in men, 50 mg/dl in women), high triglycerides (≥150 mg/dl), and Glycated hemoglobin (HbA1c) with ≥5.6 mg/dl [20].

Statistical analyses

Bivariate analyses were used to assess the association between patient characteristics and 1) LTBI and 2) Dyslipidemia. We used Chi-square tests for comparison of categorical variables, and Wilcoxon rank sum or T-tests for continuous variable comparisons. Multivariable logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between LTBI and dyslipidemia; ordinal logistic regression was used to estimate the association between LTBI and severity of dyslipidemia. Covariates included in multivariable regression models were selected based on observed associations in bivariate analyses and previous studies (factors likely confounding the LTBI-dyslipidemia association) [17, 25-27]. All analyses were conducted using SAS 9.4. A two-sided P value <0.05 was considered statistically significant for all analyses.

Ethics

This study was reviewed and approved by the Institutional Review Boards at Georgia Department of Public Health and Georgia State University.

RESULTS

During the study period, medical information of 701 refugees who received care at the DeKalb County Board of Health Refugee Clinic between 1st October 2013 and 31st August 2014 was available. A total of 684 patients met study eligibility criteria and were included in the study (Figure 1). Median participant age was 33 years (IQR 27.0-42.0) and the majority were male (55.5% vs 44.5%).

Median body mass index (BMI) was 24.0 kg/m2 (IQR 21.0-27.2), 6.5% of participants were underweight, 29.8% were overweight, and 12.1% were obese. The prevalence of pre-DM was 34.2% and DM prevalence was 7.8%.

The overall prevalence of LTBI was 31.9% (218/684) (Table 1). Participants with LTBI were older (median age 35.5 vs. 32.0), more likely to be born in countries with higher TB incidence (71.7% vs. 61.4%) and have pre-DM or DM (52.8% vs. 37.0%) compared to participants without LTBI (p value <0.05 for all comparisons).

Regarding lipid levels, the prevalence of elevated total cholesterol, low HDL-C and elevated TGL was 30.6% (209/684), 44% (301/684), and 40.7% (276/684) respectively (Table 2). Median total cholesterol was 180 mg/dl (IQR 155.5-209.0), median HDL-C was 46 mg/dl (IQR 39.0-53.5), and median TGL was 128 mg/dl (IQR 87.5-191.5). Hypercholesterolemia was more common among those who were older (median age 39 vs. 31), male (37.0% vs.22.6%), had higher BMI (median BMI 28.6 kg/m2 vs.23.5 kg/m2) and pre-DM (34.0% vs.24.5%) or DM (56.6% vs. 24.0%) (p value <0.05 for all results). Similarly, hypertriglyceridemia was higher in those who were older (median age 36 vs. 30), male (50.5% vs.27.9%), had higher BMI (median BMI 25.7 kg/m2 vs.22.9 kg/m2) and pre-DM (47.0% vs.32.8%) or DM (66% vs. 32.8%) (p value<0.05 for the all results). Prevalence of low HDL-C was higher among females (58.5% vs 32.4%), those who had higher BMI (median BMI 25.1 kg/m2 vs.23.3 kg/m2) and pre-DM (50.0% vs.38.4%) or DM (56.4% vs. 38.4%) (p value <0.05 for all results).

Compared to participants without LTBI, those with LTBI had non-significantly higher proportions of elevated total cholesterol (28.3% vs.35.3%, p value=0.06) and elevated TGL (38.4% vs. 44.5%p value=0.13). More participants with LTBI had low HDL-C levels compared to those without LTBI (40.4% vs. 45.7% p-value=0.64). A non-significantly higher proportion of any dyslipidemia was

observed among participants with LTBI compared to than those without LTBI (72.9% vs 69.8%, p value=0.39) (Table 1).

Total cholesterol was non-significantly higher among participants with LTBI (median total cholesterol 184 mg/dl, IQR 159-213) than those without LTBI (median total cholesterol 178 mg/dl, IQR 153-205) (p value=0.05). There was no difference in median HDL-C between those with LTBI (median HDL-C 46 mg/dl, IQR 38-53) and without LTBI (median HDL-C 46 mg/dl, IQR 38-53) (p value=0.19). Also, TGL was non-significantly higher in participants with LTBI (median TGL 134 mg/dl, IQR 87-202) compare to participants without LTBI (median TGL 128 mg/dl, IQR 88-188) (p value=0.35) (Table 1).

After adjusting for age, sex, body mass index and DM status, the odds of having hypercholesterolemia among those with LTBI was 1.3 (95% confidence interval [CI] 0.9-1.8) times the odds among those without LTBI (Table 3). In a similarly adjusted model, the odds of having low HDL-C was 0.77 (95% CI 0.54-1.07) times the odds of those without LTBI. Third, the odds of having elevated TGL among participants with LTBI was 1.18 (95% CI 0.84-1.67) times the odds of elevated TGL among participants without LTBI.

Additionally, LTBI was not significantly associated with elevated LDL-C, combined dyslipidemia, or metabolic syndrome (Supplementary Table 2).

Moreover, among the participants with DM, high LTBI presence was observed in those who have elevated cholesterol (46.7%), low HDL-C (50.0%) and elevated TGL (48.6%) (supp table 4.). There was significant effect of elevated cholesterol and TGL on LTBI presence among who had normal BMI (18.5-24.9 kg/m2). The odds of LTBI among with elevated cholesterol (aOR 1.88, 95% CI 1.13-3.14) was higher than ones with normal cholesterol. Similarly, odds of LTBI in those with elevated TGL was higher (aOR 1.65, 95% CI 1.03-2.65) compared to ones with normal TGL.

DISCUSSION

We found that seven in ten refugees attending a community health clinic had at least one blood lipid abnormality and nearly one in three had LTBI. Although we observed trends toward increased dyslipidemia in patients with LTBI, we did not report a statistically significant association between LTBI and elevated total cholesterol, low HDL-C, or elevated TGL. Similarly, the presence of LTBI had no significant association with degree of dyslipidemia level. However, our study observed high proportion of LTBI among the participants with DM and dyslipidemia, with half of the people with DM and dyslipidemia had LTBI.

Only a limited number of studies have previously estimated the association between TB disease or LTBI presence with blood lipid abnormalities. A propensity scores matched analysis of data from the 2011-2012 National Health Nutritional Examination Survey (NHANES) reported no significant association between LTBI defined by QFT and dyslipidemia. The prevalence of elevated total cholesterol (>200 mg/dl) was same in the group with LTBI (44.7%) as it was in the non-LTBI group (44.2%) (p value=0.8). Similar outcomes for the prevalence of elevated TGL (>150 mg/dl) (24.0% vs 28.7%, p value=0.227) and low HDL-C (<40 mg/dl) (20.0% vs.17.4%, p value=0.336) were observed among two groups [28].

Conversely, studies assessing the relationship between dyslipidemia and TB disease have reported significant differences in cholesterol levels among patients with pulmonary TB (PTB) compared to those without. For example, a retrospective cohort study, involving the adults with active PTB who received care at a Turkish Armed Forces and primary care facility reported a significantly lower lipid profile in PTB patients compared to healthy controls [29]. The PTB were (both smear positive and negative) and diagnosed regarding sputum culture, chest X-ray and clinical presentation.

Compared to those without PTB, participants with PTB had lower total cholesterol (mean total cholesterol 127.6 mg/dl vs 150.8 mmol/l), LDL-C (mean LDL-C 81.2 vs. 88.9 mg/dl) and HDL-C (mean HDL-C 30.9 mg/dl vs 42.5 mg/dl) (p value<0.05 for all comparisons). Furthermore, having lower cholesterol and HDL-C presence was correlated with degree of pulmonary damage among the participants with PTB. The patients with more radiological extend (radiological) tend to have lower cholesterol (r=-0.43, p value<0.01) and HDL-C (r=-0.60, p<0.01) [29]. An additional case-control study in Turkey, conducted among active TB patients (smear and culture positive), and patients with pneumonia and healthy controls reported the similar results [30]. TB patients had lower serum total cholesterol (mean TC 137.21 vs.164.30 mg/dl), HDL-C (mean HDL-C 33.25mg/dl vs.48.6 mg/dl), and TGL (mean TGL 66.51 vs.107.43 mg/dl) compared to the control group (p value<0.05 for all comparison) [30]. Lastly, a 2016 cohort study conducted among new TB patients, who are between 25 and 60 years old in South India showed different levels of LDL-C, TGL and HDL-C by DM status (known DM [KDM], new DM diagnosis [NDM] and without DM [NG]) [31]. Participants with TB and KDM had higher serum LDL-C (mean LDL-C 97 mg/dl vs. 87 mg/dl vs. 83 mg/dl, p value=0.004) and HDL-C (mean HDL-C 38 mg/dl vs. 33 mg/dl vs. 37 mg/dl, p value=0.013) and TGL (mean TGL 111 mg/dl vs. 100 mg/dl vs. 73 mg/dl, p value<0.001) than participants with TB and NDM and NG [31].

Despite not observing a significant association in this study between LTIB and dyslipidemia, it is plausible for existing relationship. In our study, majority of our participants was at young age, 65.3% of them aged between 25-44 years old and normal range of BMI (51.6%). Yet we observed high prevalence of dyslipidemia alongside with high prevalence of LTBI. Moreover, there are plausible mechanisms which LTIB could increase the risk of metabolic diseases. Increasing evidence suggests there is an association between LTBI and DM, but whether the relationship

results from DM increasing the risk of LTBI or vice versa has not been established. Our results suggest that if LTBI increases the risk of DM it may do so independently of dyslipidemia. We reported high prevalence of LTBI among participants with DM and dyslipidemia, encouraging the screening of LTBI among refugees with DM and dyslipidemia in clinical setting. Cholesterol does play an important role in MTB infection, serving as a source of energy for the bacteria and providing protection from host immune response which promote MTB persistence [12]. Because MTB expends cholesterol, there is a possibility that persons with LTBI who have ongoing bacterial replication may in turn have lower cholesterol levels.

Our study was subject to limitations. First, our study only included state sponsored refugees to the US, therefore our results are not widely generalizable to the US general population. Second, our study only measured blood lipid levels at one point in time. Diet, alcohol use, stress and strenuous exercise before the test may have impacted the lipid test results [32] and therefore we may have misclassified participants based on dyslipidemia status. Also, clinical information related to previous diagnosis and treatment of high cholesterol and triglycerides were not available. Third, the study was cross-sectional in nature. Hence, we were not able to determine if dyslipidemia (outcome) preceded LTBI (exposure) or assess the temporal relationship. Fourth, we used a QFT test to diagnose LTBI. Currently all LTBI tests do not directly measure MTB presence, and because QFT relies on an antigen response it is likely that some misclassification of LTBI occurred. Nonetheless, our study population consisted primarily of persons who had previous BCG vaccination and therefore the QFT was the best available LTBI test. Last, it is possible that the relatively small sample size of our study population could have affected the statistical power to detect a relationship between LTBI and dyslipidemia.

Conclusion

TB and CVD have huge burdens globally, especially in the developing countries. Prominently, suggestions on the association between TB and CVD are rising, and improved understanding of this relationship has become crucial for the public health significance. As lipids play and important role in both CVD and TB disease development, it was important to address the potential relationship between TB infection and lipid abnormalities. Even though we did not observe statistically significant associations, our study reports high prevalence of dyslipidemia and LTBI among refugees arrived in US, suggesting the further exploration on relationship between TB infection and lipid abnormalities.

REFERENCES

1. WHO. Global TB Report 2017. 2017; Available from: http://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf.
2. Houben, R.M. and P.J. Dodd, The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med, 2016. 13(10): p. e1002152.
3. WHO. Latent TB infection: Updated and Consolidated guidelines for programmatic management, WHO 2018. 2018; Available from: http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/.
4. Roth, G.A., et al., Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol, 2017. 70(1): p. 1-25.
5. Huaman, M.A., et al., Tuberculosis and risk of acute myocardial infarction: a propensity score-matched analysis. Epidemiol Infect, 2017. 145(7): p. 1363-1367.
6. Sheu, J.J., et al., Tuberculosis and the risk of ischemic stroke: a 3-year follow-up study. Stroke, 2010. 41(2): p. 244-9.
7. Wang, S.H., et al., Tuberculosis increases the risk of peripheral arterial disease: A nationwide population-based study. Respirology, 2017. 22(8): p. 1670-1676.
8. Huaman, M.A., et al., The Relationship Between Latent Tuberculosis Infection and Acute Myocardial Infarction. Clin Infect Dis, 2018. 66(6): p. 886-892.
9. Huaman, M.A., et al., Tuberculosis and Cardiovascular Disease: Linking the Epidemics. Trop Dis Travel Med Vaccines, 2015. 1.
10. Elmehdawi, R., Hypolipidemia: a word of caution. Libyan J Med, 2008. 3(2): p. 84-90.

11. Gebremicael, G., et al., Lipid Profile in Tuberculosis Patients with and without Human Immunodeficiency Virus Infection. Int J Chronic Dis, 2017. 2017: p. 3843291.
12. Brzostek, A., et al., Mycobacterium tuberculosis is able to accumulate and utilize cholesterol. J Bacteriol, 2009. 191(21): p. 6584-91.
13. Soto-Ramirez, M.D., et al., Cholesterol plays a larger role during Mycobacterium tuberculosis in vitro dormancy and reactivation than previously suspected. Tuberculosis (Edinb), 2017. 103: p. 1-9.
14. Rodriguez, J.G., et al., Global adaptation to a lipid environment triggers the dormancy-related phenotype of Mycobacterium tuberculosis. MBio, 2014. 5(3): p. e01125-14.
15. Martens, G.W., et al., Hypercholesterolemia impairs immunity to tuberculosis. Infect Immun, 2008. 76(8): p. 3464-72.
16. Orozco-Beltran, D., et al., Lipid profile, cardiovascular disease and mortality in a Mediterranean high-risk population: The ESCARVAL-RISK study. PLoS One, 2017. 12(10): p. e0186196.
17. Ahmed, H.M., et al., Primary Low Level of High-Density Lipoprotein Cholesterol and Risks of Coronary Heart Disease, Cardiovascular Disease, and Death: Results From the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol, 2016. 183(10): p. 875-83.
18. Benjamin, E.J., et al., Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation, 2017. 135(10): p. e146-e603.
19. Blumberg, H.M. and R.R. Kempker, Interferon-gamma release assays for the evaluation of tuberculosis infection. JAMA, 2014. 312(14): p. 1460-1.

20. National Institute of Health. Detection, Evaluation and Treatment of High Blood Cholesterol in Adults 2005. 2005; Available from: https://www.nhlbi.nih.gov/files/docs/resources/heart/atp-3-cholesterol-full-report.pdf.
21. American Association of Clinical Endocrinologists and American College of Endocrinology. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease 2017. 2017; Available from: https://www.aace.com/files/lipid-guidelines.pdf.
22. CDC. Defining Adult Overweight and Obesity, Center for Disease Prevention and Control. 2017; Available from: https://www.cdc.gov/obesity/adult/defining.html.
23. WHO. Global TB Report 2014. 2014.
24. American Diabetes Association. American Diabetes Care. Standards of Medical Care in Diabetes 2017. 2017; Available from: https://professional.diabetes.org/sites/professional.diabetes.org/files/media/standardofcare2017fulldeckfinal_0.pdf.
25. Chen, C., et al., High Latent TB Infection Rate and Associated Risk Factors in the Eastern China of Low TB Incidence. PLoS One, 2015. 10(10): p. e0141511.
26. Qi, L., et al., Prevalence and Risk Factors Associated with Dyslipidemia in Chongqing, China. Int J Environ Res Public Health, 2015. 12(10): p. 13455-65.
27. Ni, W.Q., et al., Serum lipids and associated factors of dyslipidemia in the adult population in Shenzhen. Lipids Health Dis, 2015. 14: p. 71.

28. Huaman, M.A., G.S. Deepe, Jr., and C.J. Fichtenbaum, Elevated Circulating Concentrations of Interferon-Gamma in Latent Tuberculosis Infection. Pathog Immun, 2016. 1(2): p. 291-303.

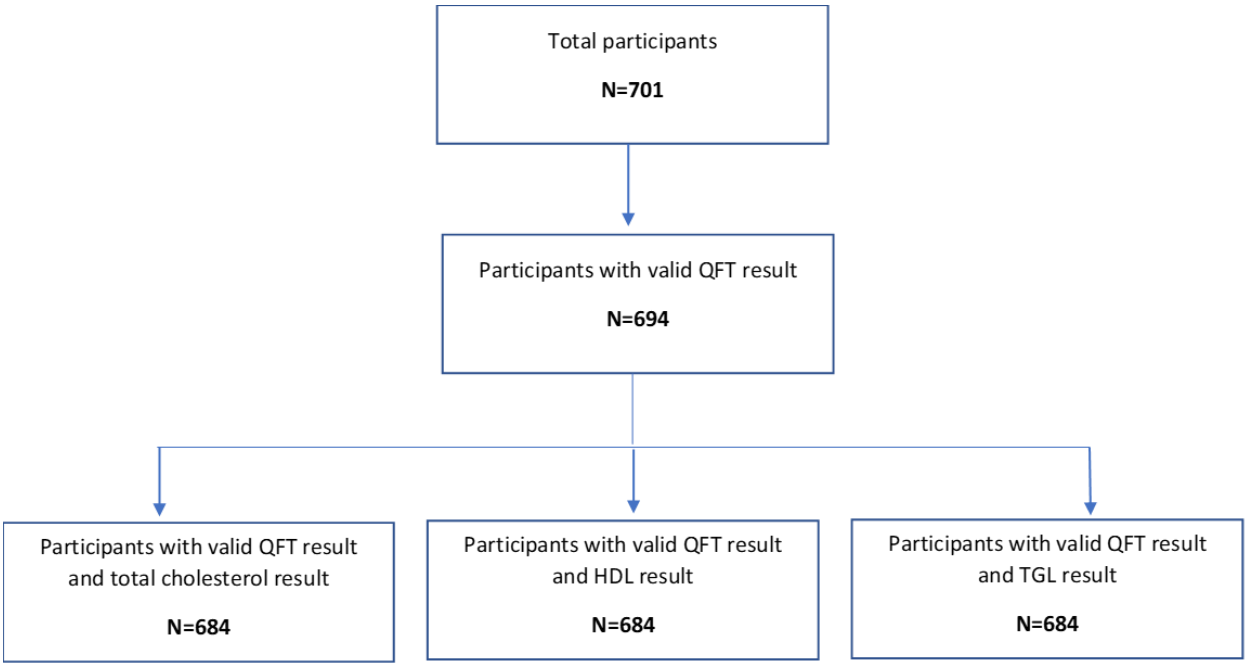
29. Deniz, O., et al., Serum total cholesterol, HDL-C and LDL-C concentrations significantly correlate with the radiological extent of disease and the degree of smear positivity in patients with pulmonary tuberculosis. Clin Biochem, 2007. 40(3-4): p. 162-6.

30. Sahin, F. and P. Yildiz, Distinctive biochemical changes in pulmonary tuberculosis and pneumonia. Arch Med Sci, 2013. 9(4): p. 656-61.

31. Kornfeld, H., et al., High Prevalence and Heterogeneity of Diabetes in Patients With TB in South India: A Report from the Effects of Diabetes on Tuberculosis Severity (EDOTS) Study. Chest, 2016. 149(6): p. 1501-8.

32. American Heart Association. Factors that influence your cholesterol lipid result. 2014; Available from: http://www.ptsdiagnostics.com/uploads/2/6/2/8/26289179/lit-001609_rev0_factors_in_lipid_testing__patient_.pdf.

Figure 1. Flow chart of study participants



LIST OF TABLES

Table 1. Characteristics of participants with LTBI, Dekalb County Refugee Clinic, 2013-2014

Characteristics	QFT negative (n= 466, 68.1%) n (%)	QFT positive (n=218, 31.9%) n (%)	Total (n=684, 100%) n (%)	p-value
Demographics				
Age, years				
Median (IQR)	32.0 (26.5-41.0)	35.5 (28.0-47.0)	33.0 (27.0-42.0)	**<0.01***
<25	75 (16.2)	22 (10.3)	97 (14.3)	
25-44	308 (66.4)	134 (62.6)	442 (65.2)	
45-64	65 (14.0)	46 (21.5)	111 (16.4)	**0.01***
≥65	16 (3.4)	12 (5.6)	28 (4.1)	
Missing	2	4	6	
Sex				
Male	252 (54.4)	124 (57.9)	376 (55.5)	
Female	211 (45.6)	90 (42.1)	301 (44.5)	0.39
Missing	3	4	7	
Country of origin				
Butan	99 (21.2)	60 (27.8)	159 (23.3)	
Burma	147 (31.6)	66 (30.6)	213 (31.2)	
Iraq	70 (15.0)	12 (5.6)	82 (12.0)	**<0.01***
Somalia	33 (7.1)	34 (15.8)	67 (9.8)	
Other	117 (25.1)	44 (20.0)	161 (23.6)	
Missing	0	2	2	
TB incidence of country of origin[#]				
<100	152 (32.6)	49 (22.7)	201 (29.5)	**<0.01***
100-299	125 (26.8)	84 (38.9)	209 (30.7)	
≥300	161 (34.6)	71 (32.8)	232 (34.0)	
Unknown	28 (6.0)	12 (5.6)	40 (5.8)	
Missing	0	2	2	
Current smoker				
No	352 (76.9)	162 (76.4)	514 (76.7)	
Yes	106 (23.1)	50 (23.6)	156 (23.3)	0.90
Missing	8	6	14	
Alcohol abuse				
No	347 (77.3)	169 (79.3)	516 (78.0)	
Yes	102 (22.7)	44 (20.7)	146 (22.0)	0.55
Missing	17	5	22	
Clinical information				
Blood pressure, mmHg				
Normal (<120/80)	235 (50.5)	113 (52.1)	348 (51.0)	
Pre-HTN (120-139/80-89)	158 (34.0)	72 (33.2)	230 (33.7)	
Stage 1-HTN (140-159/90-99)	61 (13.1)	26 (12.0)	87 (12.8)	0.95
Stage 2-HTN (>160/100)	11 (2.4)	6 (2.7)	17 (2.5)	
Missing	1	1	2	
BMI, kg/m2				
Median (IQR)	23.9 (21.1-27.1)	24.1 (20.8-27.3)	24.0 (21.0-27.2)	0.84
<18.5	29 (6.3)	15 (7.0)	44 (6.5)	
18.5-24.9	243 (52.8)	105 (48.8)	348 (51.6)	0.14
25-29.9	126 (27.4)	75 (34.9)	201 (29.8)	
≥30	62 (13.5)	20 (9.3)	82 (12.1)	
Missing	3	6	9	

DM status				
No DM	291 (63.0)	102 (47.2)	393 (58.0)	
Pre-DM	141 (30.5)	91 (42.1)	232 (34.2)	**<0.01***
DM	30 (6.5)	23 (10.7)	53 (7.8)	
Missing	4	2	6	
Hemoglobin, g/dl				
Median (IQR)	14.5 (13.0-15.6)	14.6 (13.4-15.5)	14.6 (13.1-15.6)	0.41
White blood cell, $x10^9/l$				
Median (IQR)	7.2 (5.9-8.5)	7.0 (5.8-8.2)	7.1 (5.9-8.4)	0.21
Random glucose, mg/dl				
Median (IQR)	92 (86-99)	92 (87-105)	92 (86-101)	0.14
Creatinine, mg/dl				
Median (IQR)	0.8 (0.6-0.9)	0.8 (0.6-0.9)	0.8 (0.6-0.9)	0.52
Glycated hemoglobin, %				
Median (IQR)	5.5 (5.3-5.8)	5.7 (5.4-6.0)	5.6 (5.4-5.8)	**<0.01***
Vitamin D, ng/ml				
Median (IQR)	20 (15-27)	21 (16-27)	21 (15-27)	0.46
<20	207 (44.7)	83 (38.4)	290 (42.7)	0.10
20-30	170 (36.7)	98 (45.4)	268 (39.5)	
>30	86 (18.6)	35 (16.2)	121 (17.8)	
Missing	3	2	5	
HIV status				
Negative	458 (98.7)	213 (98.2)	671 (98.5)	
Positive	6 (1.3)	4 (1.8)	10 (1.5)	0.58
Missing	2	1	3	
Syphilis, rapid plasma reagan test				
Negative	456 (97.8)	214 (98.6)	670 (98.1)	0.49
Positive	10 (2.2)	3 (1.4)	13 (1.9)	
Missing	0	1	1	
Hepatitis B, HBsAg				
Negative	453 (97.4)	212 (97.7)	665 (97.5)	
Positive	12 (2.6)	5 (2.3)	17 (2.5)	0.83
Missing	1	1	2	
Hepatitis B, HBsAb				
Negative	205 (44.1)	74 (34.1)	279 (40.9)	
Positive	260 (55.9)	143 (65.9)	403 (59.1)	**0.01***
Missing	1	1	2	
Hepatitis C, antibody				
Negative	334 (71.8)	141 (64.7)	475 (69.6)	
Positive	131 (21.2)	77 (35.3)	208 (30.4)	**0.05***
Missing	1	0	1	
Blood lipid information				
Total cholesterol, mg/dl				
Median (IQR)	178 (153-205)	184 (159-213)	180 (155.5-209)	0.15
≤130 (low)	34 (7.3)	12 (5.5)	46 (6.7)	
130< and >200 (normal)	300 (64.4)	129 (64.7)	429 (69.4)	0.06
≥200 (elevated)	132 (28.3)	77 (35.3)	209 (30.6)	
HDL-C, mg/dl $^+$				
Median (IQR)	46 (39-54)	46 (38-53)	46 (39.0-53.5)	0.19
Lower	213 (45.7)	88 (40.4)	301 (44.0)	0.64
Normal	253 (54.3)	130 (59.6)	383 (56.0)	
TGL, mg/dl				
Median (IQR)	127 (88-188)	134 (87-202)	128 (87.5-191.5)	0.35
<150 (normal)	287 (61.6)	121 (55.5)	408 (59.7)	0.13
≥150 (elevated)	179 (38.4)	97 (44.5)	276 (40.3)	

Total Cholesterol (log)				
Mean (SD)	5.18 (0.21)	5.21 (0.21)	5.19 (0.21)	**0.05***
HDL-C (log)				
Mean (SD)	3.81 (0.24)	3.80 (0.25)	3.81 (0.24)	0.57
TGL (log)				
Median (IQR)	4.8 (4.5-5.2)	4.9 (4.5-5.3)	4.85 (4.5-5.3)	0.35
Total cholesterol level, mg/dl				
Normal (160-199)	334 (71.7)	141 (64.7)	475 (69.4)	
Borderline high (200-239)	89 (19.1)	47 (21.6)	136 (19.9)	
High (≥240)	43 (9.2)	30 (13.7)	73 (10.7)	0.11
TGL level, mg/dl				
Optimal (<150)	287 (61.6)	121 (55.5)	408 (59.6)	
Borderline high (150-199)	75 (16.1)	42 (19.3)	117 (17.1)	0.31
High (≥200)	104 (22.3)	55 (25.2)	159 (23.3)	
Any dyslipidemia ++				
Yes	325 (69.8)	159 (72.9)	484 (70.8)	0.39
No	142 (30.2)	59 (27.1)	200 (29.2)	

*****-Statistically significant, Chi-square (categorical) or Wilcoxon test (medians) or T-test (means), two-sided p-value <0.05

#- Incidence of active TB case per 100 000 population, WHO Global Tuberculosis Report 2014

+- HDL-C defined different in male and female. Lower (<40 mg/dl in male, <50 mg/dl in female) and normal (≥40 mg/dl in male, ≥50 mg/dl in female)

++-Any dyslipidemia defined as elevated total cholesterol (≥200 mg/dl) OR lower HDL-C (<40 mg/dl in male, <50 mg/dl in female) OR elevated TGL (≥150 mg/dl)

LTBI= Latent TB Infection, QFT= QuantiFERON®-TB Gold in-Tube test, IQR=Interquartile range, TB=Tuberculosis, HTN=Hypertension, BMI=Body mass index, DM=Diabetes Mellitus, HIV=Human immunodeficiency virus, HBsAg= Hepatitis B surface antigen, HBsAb= Hepatitis surface antibody, HDL-C =High density lipoprotein, TGL=Triglycerides, SD=Standard Deviation, WHO-World Health Organization.

Table 2. Characteristics of participants by total cholesterol, HDL-C and TGL, Dekalb County Refugee Clinic, 2013-2014

Characteristics	Total Cholesterol[+]			HDL-C[++]			TGL[+++]		
	Normal	**Elevated**	p-value	**Normal**	**Lower**	p-value	**Normal**	**Elevated**	p-value
	n=475 (69.4%) n (%)	n=209 (30.6%) n (%)		n=383 (56.0%) n (%)	n=301 (44.0%) n (%)		n=408 (59.7%) n (%)	n=276 (40.7%) n (%)	
Demographics									
Age, years									
Median (IQR)	31 (26-39)	39 (31-50)	**<0.01***	32 (26-41)	33 (27-44)	0.12	30 (25-39)	36 (29-50)	**<0.01***
<25	81 (83.5)	16 (16.5)		57 (58.8)	40 (41.2)		74 (76.3)	23 (23.7)	
25-44	320 (72.4)	122 (27.6)		249 (56.3)	193 (43.7)		274 (62.0)	168 (38.0)	
45-64	55 (49.6)	56 (50.4)	**<0.01***	56 (50.4)	55 (49.6)	0.63	42 (37.8)	69 (62.2)	**<0.01***
≥65	16 (57.1)	12 (42.9)		15 (53.6)	13 (46.4)		13 (46.4)	15 (53.6)	
Missing	3	3		6	0		5	1	
Sex									
Male	237 (63.0)	139 (37.0)	**<0.01***	254 (67.6)	122 (32.4)	**<0.01***	186 (49.5)	190 (50.5)	**<0.01***
Female	233 (77.4)	68 (22.6)		125 (41.5)	176 (58.5)		217 (72.1)	84 (27.9)	
Missing	5	2		4	3		5	2	
Country of origin[#]									
Butan	104 (65.4)	55 (34.6)	0.11	83 (52.2)	76 (47.8)	**<0.01***	78 (49.1)	81 (50.9)	0.05
Burma	139 (65.3)	74 (34.7)		129 (60.6)	84 (29.4)		132 (62.0)	81 (38.0)	
Iraq	62 (75.6)	20 (24.4)		36 (43.9)	46 (56.1)		51 (62.2)	31 (37.8)	
Somalia	47 (70.2)	20 (29.8)		31 (46.3)	36 (53.7)		43 (64.2)	24 (36.8)	
Other	122 (75.8)	39 (24.2)		102 (63.4)	59 (36.6)		102 (63.4)	59 (36.6)	
Missing	1	1		2	0		2	0	
TB incidence of country of origin[#]									
<100	144 (71.6)	57 (28.4)		101 (50.2)	100 (49.8)		122 (60.7)	79 (39.3)	
100-299	147 (70.3)	62 (29.7)		108 (51.7)	101 (48.3)		111 (53.1)	98 (46.9)	
≥300	155 (66.8)	77 (33.2)	0.73	142 (61.2)	90 (38.8)	**<0.01***	145 (62.5)	87 (37.5)	
Unknown	28 (70.0)	12 (30.0)		30 (75.0)	10 (25.0)		28 (70.0)	12 (30.0)	
Missing	1	1		2	0		2	0	
Current smoker									
No	362 (70.4)	152 (29.6)		286 (55.6)	228 (44.4)		323 (62.8)	191 (37.2)	
Yes	101 (64.7)	55 (35.3)	0.18	88 (56.4)	68 (43.4)	0.86	74 (47.4)	82 (52.6)	**<0.01***
Missing	12	2		9	5		11	3	
Alcohol abuse									
No	369 (71.5)	147 (28.5)		277 (53.7)	239 (46.3)		326 (63.2)	190 (39.8)	
Yes	87 (59.6)	59 (40.4)	**<0.01***	98 (67.1)	48 (32.9)	**<0.01***	67 (45.9)	79 (54.1)	**<0.01***
Missing	19	3		8	14		15	7	

Clinical information

Blood pressure, mmHg									
Normal (<120/80)	269 (77.3)	79 (22.7)		189 (54.3)	159 (46.7)		254 (73.0)	94 (27.0)	
Pre-HTN (120-139/80-89)	143 (62.2)	87 (37.8)		136 (59.1)	94 (40.9)		114 (49.6)	116 (50.4)	
Stage 1-HTN (140-159/90-99)	51 (58.6)	36 (41.4)	**<0.01***	47 (54.0)	40 (46.0)	0.67	31 (35.6)	56 (64.4)	**<0.01***
Stage 2-HTN (>160/100)	10 (58.2)	7 (41.2)		9 (47.1)	8 (52.9)		7 (41.2)	10 (58.8)	
Missing	2	0		0	2		2	0	
BMI, kg/m2									
Median (IQR)	23.5 (20.6-26.6)	28.6 (22.6-28.3)	**<0.01***	23.3 (20.5-26.1)	25.1 (22.0-28.4)	**<0.01***	22.9 (20.3-26.3)	25.7 (22.9-28.2)	**<0.01***
<18.5	41 (79.6)	12 (20.4)		30 (68.2)	14 (31.8)		38 (86.4)	6 (13.6)	
18.5-24.9	262 (75.3)	86 (24.7)	**<0.01***	215 (61.8)	133 (38.2)	**<0.01***	230 (66.1)	118 (33.9)	**<0.01***
25-29.9	126 (69.7)	75 (30.3)		99 (49.3)	102 (50.7)		96 (47.7)	105 (52.3)	
≥30	46 (56.1)	36 (43.9)		33 (40.2)	49 (59.8)		38 (46.3)	44 (53.6)	
Missing	5	4		3	6		6	3	
DM status									
No DM	293 (74.5)	100 (24.5)		242 (61.6)	151 (38.4)		264 (67.2)	129 (32.8)	
Pre-DM	153 (66.0)	79 (34.0)	**<0.01***	116 (50.0)	116 (50.0)	**<0.01***	123 (53.0)	109 (47.0)	**<0.01***
DM	23 (43.4)	30 (56.6)		23 (43.4)	30 (56.4)		18 (34.0)	35 (66.0)	
Missing	6	0		2	4		3	3	
Hemoglobin, g/dl									
Median (IQR)	14.1 (12.9-15.5)	15.1 (13.9-16.0)	**<0.01***	14.8 (13.5-15.6)	14.0 (12.7-15.5)	**<0.01***	13.9 (12.8-15.3)	15.1 (13.9-16.0)	**<0.01***
White blood cell, x10^9/l									
Median (IQR)	7.1 (5.7-8.2)	7.3 (6.1-8.6)	0.06	7.0 (5.7-8.3)	7.2 (6.1-8.5)	0.07	6.8 (5.6-7.9)	7.5 (6.4-8.8)	**<0.01***
Random glucose, mg/dl									
Median (IQR)	91 (85-98)	95 (88-106)	**<0.01***	92 (86-99)	92 (85-104)	0.71	90 (85-97)	95 (88-106)	**<0.01***
Creatinine, mg/dl									
Median (IQR)	0.8 (0.6-0.9)	0.9 (0.7-1.0)	**<0.01***	0.8 (0.7-0.9)	0.7 (0.6-0.9)	**<0.01***	0.7 (0.6-0.9)	0.9 (0.7-1.0)	**<0.01***

Glycated hemoglobin, %									
Median (IQR)	5.5 (5.3-5.8)	5.7 (5.4-6.0)	**<0.01***	5.5 (5.3-5.8)	5.6 (5.4-5.9)	**<0.01***	5.5 (5.3-5.7)	5.7 (5.4-6.0)	**<0.01***
Vitamin D, ng/ml									
Median (IQR)	20 (15-26)	22 (16-28)	0.06	21 (16-28)	20 (14-25)	**<0.01***	20 (15-26)	22 (16-28)	**0.01***
<20	214 (73.8)	76 (26.2)		149 (51.4)	141 (48.6)		186 (64.1)	104 (35.9)	
20-30	178 (66.4)	90 (33.6)	0.08	156 (58.2)	112 (41.8)	0.11	157 (58.6)	111 (41.4)	
>30	78 (64.5)	43 (35.6)		74 (61.2)	47 (38.8)		62 (51.2)	59 (48.8)	
Missing	5	0		1	4		3	2	
HIV status									
Negative	465 (69.3)	206 (30.7)	0.96	375 (55.9)	296 (44.1)	0.71	398 (59.3)	273 (40.7)	0.49
Positive	7 (70.0)	3 (30.0)		5 (50.0)	5 (50.0)		7 (70.0)	3 (30.0)	
Missing	3	0		3	0		3	0	
Syphilis, rapid plasma reagan test									
Negative	466 (69.6)	204 (30.4)	0.53	373 (55.7)	297 (44.3)	0.33	400 (59.7)	270 (40.3)	0.67
Positive	8 (61.5)	5 (38.5)		9 (69.2)	4 (30.2)		7 (53.9)	6 (46.1)	
Missing	1	0		1	0		1	0	
Hepatitis B, HBsAg									
Negative	462 (69.5)	203 (30.5)	0.67	371 (55.8)	294 (44.2)	0.8	391 (58.8)	274 (41.2)	**0.01***
Positive	11 (64.7)	6 (35.3)		10 (58.8)	7 (41.2)		15 (88.2)	2 (11.8)	
Missing	2	0		2	0		2	0	
Hepatitis B, HBsAb									
Negative	203 (72.8)	76 (27.2)	0.11	153 (54.8)	126 (45.2)	0.61	187 (67.0)	92 (33.0)	**<0.01***
Positive	270 (67.0)	133 (33.0)		229 (56.8)	174 (43.2)		220 (54.6)	183 (45.4)	
Missing	2	0		1	1		1	1	
Hepatitis C, antibody									
Negative	340 (71.6)	135 (28.4)	0.06	268 (56.4)	207 (43.6)	0.7	284 (59.8)	191 (40.2)	0.87
Positive	134 (64.4)	74 (35.6)		114 (54.8)	94 (45.2)		123 (59.1)	85 (40.9)	
Missing	1			1	0		1		

LTBI									
QFT Negative	334 (71.7)	132 (28.3)	0.06	253 (54.3)	213 (46.7)	0.19	287 (61.6)	179 (38.4)	0.13
QFT Positive	141 (64.7)	77 (35.3)		130 (59.6)	88 (40.4)		121 (55.5)	97 (44.5)	

+- Total cholesterol defined as normal (<200 mg/dl) and elevated (≥200 mg/dl).
++- HDL-C defined different in male and female. Normal (≥40 mg/dl in male, ≥50 mg/dl in female) and lower (<40 mg/dl in male, <50 mg/dl in female).
+++- TGL defined as normal (<150 mg/dl) and elevated (≥150 mg/dl).
*****-Statistically significant, Chi-square (categorical) or Wilcoxon test (medians), two-sided p-value <0.05
#- Incidence of active TB case per 100 000 population, WHO Global Tuberculosis Report 2014
IQR=Interquartile range, TB=Tuberculosis, HTN=Hypertension, BMI= Body mass index, DM=Diabetes Mellitus, HIV=Human immunodeficiency virus, HBsAg= Hepatitis B surface antigen, HBsAb= Hepatitis surface antibody, HDL-C =High density lipoprotein, TGL=Triglycerides, LTBI= Latent TB Infection, QFT= QuantiFERON®-TB Gold in-Tube test, WHO-World Health Organization.

Table 3. Association between latent TB infection and dyslipidemia (total cholesterol, HDL-C and TGL)

	Crude OR (95% CI)	Adjusted OR (95% CI) *
TOTAL CHOLESTEROL		
Odds of total cholesterol as ≥ 200 mg/dl (binary logistic regression, n=684)		
LTBI negative	Ref	Ref
LTBI positive	1.38 (0.98-1.95)	1.27 (0.89-1.82)
Odds of total cholesterol as 200-239 mg/dl and ≥240 mg/dl (ordinal logistic regression, n=684)		
LTBI negative	Ref	Ref
LTBI positive	1.41 (1.01-1.97)	1.31 (0.93-1.86)
HDL-C		
Odds of HDL-C as ≤ 40 mg/dl in male and ≤ 50 mg/dl in female (binary logistic regression, n=684)		
LTBI negative	Ref	Ref
LTBI positive	0.80 (0.58-1.11)	0.77 (0.54-1.07)
TGL		
Odds of TGL ≥ as 150 mg/dl (binary logistic regression, n=684)		
LTBI negative	Ref	Ref
LTBI positive	1.29 (0.93-1.78)	1.18 (0.84-1.67)
Odds of TGL as 150-199 mg/dl and ≥200 mg/dl (ordinal logistic regression, n=684)		
LTBI negative	Ref	Ref
LTBI positive	1.25 (0.91-1.71)	1.13 (0.81-1.56)

*****-Adjusted for age group, gender, body mass index, and diabetes mellitus
#-Only binary logistic regression analysis was conducted on HDL-C
-Missing values of covariates were coded as level of covariates
LTBI= Latent TB Infection, HDL-C =High density lipoprotein, TGL=Triglycerides, OR=Odds ratio, CI=Confidence interval

Supplemental Table 1. Characteristics of participants by LDL-C, Metabolic syndrome and Combined dyslipidemia, Dekalb County, Refugee Clinic

Characteristics	LDL-C[+]			Metabolic syndrome[++]			Combined Dyslipidemia[+++]		
	Normal	**Elevated**	p-value	**No**	**Yes**	p-value	**No**	**Yes**	p-value
	n=514 (78.5%) n (%)	n=141 (21.5%) n (%)		n=653 (96.3%) n (%)	n=25 (3.7%) n (%)		n=572 (87.3%) n (%)	n=83 (12.7%) n (%)	
Demographics									
Age, years									
Median (IQR)	31 (26-40)	39 (29-50)	**<0.01***	33 (27-42)	39 (27-53)	0.06	30 (25-39)	36 (29-50)	**<0.01***
<25	82 (84.5)	15 (15.5)		93 (96.9)	3 (3.1)		91 (93.8)	6 (6.2)	
25-44	342 (81.8)	76 (18.2)		428 (97.5)	11 (2.5)		378 (90.4)	40 (9.6)	
45-64	65 (60.8)	42 (39.2)	**<0.01***	101 (91.8)	9 (8.1)	**0.03***	77 (72.0)	30 (28.0)	**<0.01***
≥65	21 (77.8)	6 (22.2)		26 (92.9)	2 (7.1)		21 (77.8)	6 (22.2)	
Missing	4	2		5	0		5	1	
Sex									
Male	263 (74.7)	89 (82.8)	**0.01***	358 (96.0)	15 (4.0)	0.48	298 (84.7)	54 (5.3)	**0.02***
Female	245 (25.3)	51 (17.2)		289 (97.0)	9 (3.0)		268 (90.5)	28 (9.5)	
Missing	6	1		6	1		6	1	
Country of origin[#]									
Butan	114 (76.0)	36 (24.0)	0.57	125 (83.3)	25 (16.7)	0.55	152 (96.8)	5 (3.2)	0.34
Burma	157 (77.0)	47 (23.0)		179 (87.8)	25 (12.2)		207 (98.1)	4 (1.9)	
Iraq	65 (83.3)	13 (16.7)		69 (88.5)	9 (14.5)		77 (93.9)	5 (6.1)	
Somalia	50 (75.8)	16 (24.2)		58 (87.9)	8 (12.1)		63 (94.0)	4 (6.0)	
Other	126 (81.3)	29 (18.8)		139 (89.7)	16 (10.3)		153 (95.6)	7 (4.4)	
Missing	2	0		0	2		0	1	
TB incidence of country of origin[#]									
<100	153 (78.9)	41 (21.1)	0.98	191 (95.0)	10 (5.0)	0.60	170 (87.6)	24 (12.4)	0.80
100-299	157 (78.9)	42 (21.1)		200 (96.6)	7 (3.4)		170 (85.4)	29 (14.6)	
≥300	171 (77.7)	49 (22.3)		223 (97.4)	6 (2.6)		195 (88.6)	25 (11.4)	
Unknown	31 (77.5)	9 (22.5)		38 (95.0)	2 (5.0)		35 (87.5)	5 (12.5)	
Missing	2	0		1	0		2	0	
Current smoker									
No	392 (79.0)	104 (30.0)		497 (97.1)	10 (2.9)		436 (87.9)	60 (2.1)	
Yes	110 (75.9)	35 (24.1)	0.41	145 (93.6)	15 (6.4)	**0.04***	123 (84.8)	22 (5.2)	0.33
Missing	12	2		11	0		13	1	
Alcohol abuse									
No	397 (79.9)	100 (20.1)		493 (96.3)	19 (3.7)		442 (88.9)	55 (11.1)	
Yes	98 (71.5)	39 (28.5)	**0.04***	140 (95.9)	6 (4.1)	0.82	110 (80.3)	27 (19.7)	**<0.01***
Missing	19	2		20	0		20	1	

Clinical information

Blood pressure, mmHg									
Normal (<120/80)	280 (82.4)	60 (17.6)		345 (100.0)	0 (0.0)		312 (91.8)	28 (8.2)	
Pre-HTN (120-139/80-89)	161 (74.9)	54 (25.1)		229 (100.0)	0 (0.0)		181 (84.2)	34 (15.8)	
Stage 1-HTN (140-159/90-99)	61 (74.4)	21 (25.6)	**0.05***	68 (78.2)	19 (21.8)	**<0.01***	66 (80.5)	16 (19.5)	**<0.01***
Stage 2-HTN (>160/100)	10 (62.5)	6 (37.5)		11 (64.7)	6 (35.3)		11 (68.8)	5 (31.2)	
Missing	2	0		2	0		2	0	
BMI, kg/m2									
Median (IQR)	23.4 (20.6-26.7)	25.7 (22.6-28.4)	**<0.01***	23.9 (21.0-27.1)	27.7 (24.2-30.7)	**<0.01***	22.9 (20.3-26.3)	25.7 (22.9-28.2)	**<0.01***
<18.5	39 (88.6)	5 (11.4)		44 (100.0)	0 (0.0)		42 (95.4)	2 (4.6)	
18.5-24.9	281 (82.9)	58 (17.1)	**<0.01***	336 (97.4)	9 (2.6)	0.09	309 (91.2)	30 (8.8)	**<0.01***
25-29.9	137 (73.7)	49 (26.3)		191 (95.5)	9 (4.5)		153 (82.3)	33 (17.7)	
≥30	50 (65.0)	27 (35.0)		76 (92.7)	6 (7.3)		61 (79.2)	16 (20.8)	
Missing	7	2		6	1		7	2	
DM status									
No DM	311 (82.5)	66 (17.5)		388 (99.2)	3 (0.8)		345 (91.5)	32 (8.5)	
Pre-DM	169 (76.1)	53 (23.9)	**<0.01***	218 (94.0)	14 (6.0)	**<0.01***	188 (84.7)	34 (15.3)	**<0.01***
DM	29 (58.0)	21 (42.0)		45 (84.9)	8 (15.1)		33 (66.0)	17 (34.0)	
Missing	5	0		2	0		6	0	
Hemoglobin, g/dl									
Median (IQR)	14.3 (13.0-15.5)	14.9 (13.6-15.9)	**<0.01***	14.5 (13.1-15.6)	15.1 (14.0-16.1)	0.09	13.9 (12.8-15.3)	15.1 (13.9-16.0)	**<0.01***
White blood cell, x10^9/l									
Median (IQR)	7.1 (5.7-8.3)	7.1 (6.0-8.4)	0.38	7.1 (5.9-8.4)	7.8 (7.0-8.9)	0.10	6.8 (5.6-7.9)	7.5 (6.4-8.8)	**<0.01***
Random glucose, mg/dl									
Median (IQR)	91 (85-99)	94 (86-105)	**0.01***	92 (86-100)	109 (94-138)	**<0.01***	90 (85-97)	95 (88-106)	**<0.01***
Creatinine, mg/dl									
Median (IQR)	0.8 (0.6-0.9)	0.8 (0.7-1.0)	**<0.01***	0.8 (0.6-0.9)	0.9 (0.8-1.0)	**<0.01***	0.74 (0.60-0.87)	0.86 (0.72-0.96)	**<0.01***
Glycated hemoglobin, %									
Median (IQR)	5.5 (5.3-5.8)	5.7 (5.4-6.0)	**<0.01***	5.6 (5.4-5.8)	5.9 (5.8-6.5)	**<0.01***	5.5 (5.3-5.7)	5.7 (5.4-6.0)	**<0.01***
Vitamin D, ng/ml									
Median (IQR)	20 (15-27)	23 (16-29)	**0.04***	21 (15-27)	20 (15-30)	0.90	20 (15-26)	22 (16-28)	**0.01***
<20	231 (83.1)	47 (16.9)		274 (95.8)	12 (4.2)		248 (89.2)	30 (10.8)	
20-30	196 (76.9)	59 (23.1)	**0.01***	262 (98.1)	5 (1.9)	0.06	223 (87.5)	32 (12.6)	
>30	82 (70.1)	35 (29.9)		112 (93.3)	8 (6.7)		96 (82.1)	21 (17.9)	
Missing	5	0		5	0		5	0	
HIV status									
Negative	503 (78.4)	139 (21.6)		640 (96.2)	25 (3.8)		560 (87.2)	82 (12.8)	
Positive	8 (80.0)	2 (20.0)	0.90	10 (100.0)	0 (0.0)	0.53	9 (90.0)	1 (10.0)	0.79
Missing	3	0		3	0		3	0	

Syphilis, rapid plasma 41eagan test									
Negative	502 (78.3)	139 (21.7)		639 (96.2)	25 (3.8)		559 (87.2)	82 (12.8)	
Positive	11 (84.6)	2 (15.4)	0.58	13 (100.0)	0 (0.0)	0.33	12 (92.3)	1 (7.7)	0.58
Missing	1	0		1	0		1	0	
Hepatitis B, HbsAg									
Negative	501 (78.7)	136 (21.3)		634 (96.2)	25 (3.8)		554 (87.0)	83 (13.0)	
Positive	11 (68.8)	5 (31.2)	0.34	17 (100.0)	0 (0.0)	0.41	16 (100.0)	0 (0.0)	**0.01***
Missing	2	0		2	0		2	0	
Hepatitis B, HbsAb									
Negative	218 (82.0)	48 (18.0)		270 (97.1)	8 (2.9)		241 (90.6)	25 (9.4)	
Positive	295 (76.0)	93 (24.0)	0.07	381 (95.7)	17 (4.3)	0.34	330 (85.1)	58 (14.9)	**0.04***
Missing	1	0		2	0		1	0	
Hepatitis C, antibody									
Negative	366 (80.6)	88 (19.4)		456 (97.2)	13 (2.8)		398 (87.7)	56 (12.3)	
Positive	147 (73.5)	53 (26.5)	**0.04***	196 (94.2)	92 (5.8)	0.06	173 (86.5)	27 (13.5)	0.68
Missing	1			1	0		1		
LTBI									
QFT Negative	359 (80.0)	90 (20.0)	0.17	446 (96.3)	17 (3.7)	0.98	396 (88.2)	53 (11.8)	0.13
QFT Positive	155 (75.0)	51 (25.0)		207 (96.3)	8 (3.7)		176 (85.4)	30 (14.6)	

+- LDL-C defined as normal (<130 mg/dl) and elevated (≥130 mg/dl).

++- Metabolic syndrome defined as Stage 1 (140-159/90-99 mmHg) or Stage 2 Hypertension (>160/100 mmHg) AND elevated TGL (≥150 mg/dl) AND low HDL-C (<40 mg/dl in male, <50 mg/dl in female) AND Glycated hemoglobin (≥5.6%).

+++- Combined dyslipidemia defined as elevated LDL-C (≥130 mg/dl) AND elevated TGL (≥150 mg/dl).

*****-Statistically significant, Chi-square (categorical) or Wilcoxon test (medians), two-sided p-value <0.05

#- Incidence of active TB case per 100 000 population, WHO Global Tuberculosis Report 2014

LDL-C=Low density lipoprotein, IQR=Interquartile range, TB=Tuberculosis, HTN=Hypertension, BMI= Body mass index, DM=Diabetes Mellitus, HIV=Human immunodeficiency virus, HBsAg= Hepatitis B surface antigen, HBsAb= Hepatitis surface antibody, LTBI= Latent TB Infection, QFT= QuantiFERON®-TB Gold in-Tube test, HDL-C= High density lipoprotein, TGL=Triglycerides, WHO-World Health Organization.

Supplemental Table 2. Binary association between LTBI and LDL-C, Metabolic Syndrome and Combined dyslipidemia

	Crude OR (95% CI)	Adjusted OR (95%)*
Odds of LDL-C as ≥130 mg/dl (n=655)		
LTBI negative	Ref	Ref
LTBI positive	1.31 (0.89-1.94)	1.22 (0.82-1.83)
Odds of metabolic syndrome (n=678)		
LTBI negative	Ref	Ref
LTBI positive	1.01 (0.43-2.39)	0.92 (0.38-2.23)
Odds of combined dyslipdemia (n=655)		
LTBI negative	Ref	Ref
LTBI positive	1.27 (0.79-2.06)	1.14 (0.69-1.88)

***-**Adjusted for age group, gender, body mass index, and diabetes mellitus
+- LDL -Cdefined as normal (<130 mg/dl) and elevated (≥130 mg/dl).
++- Metabolic syndrome defined as Stage 1 (140-159/90-99 mmHg) or Stage 2 Hypertension ((>160/100 mmHg) AND elevated TGL (≥150 mg/dl) AND low HDL-C (<40 mg/dl in male, <50 mg/dl in female) AND Glycated hemoglobin (≥5.6%).
+++- Combined dyslipidemia defined as elevated LDL-C (≥130 mg/dl) AND elevated TGL (≥150 mg/dl).
-Missing values of covariates were coded as level of covariates
LTBI= Latent TB Infection, LDL-C = density lipoprotein, OR=Odds ratio, CI=Confidence interval.

Supplemental Table 3. Latent TB infection and interaction between age group and body mass index with dyslipidemia

Age group	Lipid level	Prevalence LTBI	OR (95%CI)
<25 years old	Elevated total cholesterol (≥200 mg/dl)	31.3%	1.71 (0.52-5.60)
	Normal total cholesterol (<200 mg/dl	21.0%	
25-44 years old	Elevated total cholesterol (≥200 mg/dl)	33.6%	1.23 (0.79-1.93)
	Normal total cholesterol (<200 mg/dl	29.1%	
45-64 years old	Elevated total cholesterol (≥200 mg/dl)	42.9%	1.12 (0.53-2.40)
	Normal total cholesterol (<200 mg/dl	40.0%	
≥65 years old	Elevated total cholesterol (≥200 mg/dl)	43.8%	0.92 (0.20-4.18)
	Normal total cholesterol (<200 mg/dl	41.7%	
<25 years old	Lower HDL-C*	20.0%	1.30 (0.49-3.48)
	Normal HDL-C**	24.6%	
25-44 years old	Lower HDL-C*	28.0%	1.22 (0.81-1.84)
	Normal HDL-C**	32.1%	
45-64 years old	Lower HDL-C*	41.8%	0.97 (0.46-2.06)
	Normal HDL-C**	41.1%	
≥65 years old	Lower HDL-C*	23.1%	5.0 (0.96-26.12)
	Normal HDL-C**	60.0%	
<25 years old	Elevated triglycerides (≥150 mg/dl)	17.4%	0.66 (0.20-2.18)
	Normal triglycerides (<150 mg/dl)	24.3%	
25-44 years old	Elevated triglycerides (≥150 mg/dl)	30.9%	1.05 (0.69-1.59)
	Normal triglycerides (<150 mg/dl)	29.9%	
45-64 years old	Elevated triglycerides (≥150 mg/dl)	47.8%	2.05 (0.91-4.58)
	Normal triglycerides (<150 mg/dl)	31.0%	
≥65 years old	Elevated triglycerides (≥150 mg/dl)	46.7%	1.40 (0.31-6.33)
	Normal triglycerides (<150 mg/dl)	38.5%	

BMI	Lipid level	Prevalence LTBI	OR (95%CI)
<18.5 kg/m2	Elevated total cholesterol (≥200 mg/dl)	22.2%	0.48 (0.90-2.69)
	Normal total cholesterol (<200 mg/dl	37.1%	
18.5-24.9 kg/m2	Elevated total cholesterol (≥200 mg/dl)	26.7%	1.88 (1.13-3.14)
	Normal total cholesterol (<200 mg/dl	40.7%	
25-29.9 kg/m2	Elevated total cholesterol (≥200 mg/dl)	41.3%	1.31 (0.73-2.36)
	Normal total cholesterol (<200 mg/dl	34.9%	
≥30 kg/m2	Elevated total cholesterol (≥200 mg/dl)	23.9%	1.06 (0.39-2.92)
	Normal total cholesterol (<200 mg/dl)	25.0%	
<18.5 kg/m2	Lower HDL-C*	35.7%	0.90 (0.24-3.41)
	Normal HDL-C**	33.3%	
18.5-24.9 kg/m2	Lower HDL-C*	27.1%	1.27 (0.79-2.05)
	Normal HDL-C**	32.1%	
25-29.9 kg/m2	Lower HDL-C*	33.3%	1.41 (0.80-2.51)
	Normal HDL-C**	41.4%	
≥30 kg/m2	Lower HDL-C*	24.5%	0.99 (0.35-2.76)
	Normal HDL-C**	24.2%	
<18.5 kg/m2	Elevated triglycerides (≥150 mg/dl)	16.7%	0.34 (0.34-3.24)
	Normal triglycerides (<150 mg/dl)	36.8%	
18.5-24.9 kg/m2	Elevated triglycerides (≥150 mg/dl)	37.3%	1.65 (1.03-2.65)
	Normal triglycerides (<150 mg/dl)	26.5%	
25-29.9 kg/m2	Elevated triglycerides (≥150 mg/dl)	39.1%	1.17 (0.66-2.07)
	Normal triglycerides (<150 mg/dl)	35.4%	
≥30 kg/m2	Elevated triglycerides (≥150 mg/dl)	25.0%	1.07 (0.39-3.00)
	Normal triglycerides (<150 mg/dl)	23.4%	

*Lower HDL-C (<40 mg/dl in male, <50 mg/dl in female)

**Normal HDL-C (≥40 mg/dl in male, ≥50 mg/dl in female)

Supplemental Table 4. Latent TB infection and interaction between diabetes and vitamin D with dyslipidemia

	Lipid level	Prevalence LTBI	OR (95%CI)
DM-yes	Elevated total cholesterol (≥200 mg/dl)	46.7%	1.36 (0.45-4.10)
	Normal total cholesterol (<200 mg/dl)	39.1%	
DM-no	Elevated total cholesterol (≥200 mg/dl)	31.1%	1.41 (0.85-2.32)
	Normal total cholesterol (<200 mg/dl)	24.2%	
Vitamin D-low	Elevated total cholesterol (≥200 mg/dl)	32.9%	1.32 (0.75-2.32)
	Normal total cholesterol (<200 mg/dl)	27.1%	
Vitamin D-normal	Elevated total cholesterol (≥200 mg/dl)	39.1%	1.39 (0.90-2.15)
	Normal total cholesterol (<200 mg/dl)	31.6%	
DM-yes	Lower HDL-C*	50.0%	0.53 (0.17-1.63)
	Normal HDL-C**	34.8%	
DM-no	Lower HDL-C*	20.5%	1.6 (0.99-2.60)
	Normal HDL-C**	29.3%	
Vitamin D-low	Lower HDL-C*	26.2%	1.26 (0.75-2.09)
	Normal HDL-C**	30.9%	
Vitamin D-normal	Lower HDL-C*	32.1%	1.39 (0.90-2.15)
	Normal HDL-C**	35.7%	
DM-yes	Elevated triglycerides (≥150 mg/dl)	48.6%	1.89 (0.58-6.17)
	Normal triglycerides (<150 mg/dl)	33.3%	
DM-no	Elevated triglycerides (≥150 mg/dl)	28.7%	1.23 (0.77-1.98)
	Normal triglycerides (<150 mg/dl)	24.6%	
Vitamin D-low	Elevated triglycerides (≥150 mg/dl)	33.6%	1.46 (0.87-2.46)
	Normal triglycerides (<150 mg/dl)	25.8%	
Vitamin D-normal	Elevated triglycerides (≥150 mg/dl)	35.3%	1.09 (0.71-1.66)
	Normal triglycerides (<150 mg/dl)	33.3%	

*Lower HDL-C (<40 mg/dl in male, <50 mg/dl in female)
*Normal HDL-C (≥40 mg/dl in male, ≥50 mg/dl in female)