FASTING SERUM GROWTH HORMONE LEVELS IN NEWLY DIAGNOSED PATIENTS OF PULMONARY TUBERCULOSIS WITH AND WITHOUT COEXISTENT DIABETES MELLITUS TYPE2

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ABSTRACT

The aim of this cross-sectional comparative study was to determine and compare the serum growth hormone (GH) and fasting blood glucose (FBG) levels in the newly diagnosed patients of pulmonary tuberculosis (TB) with and without diabetes mellitus type2 (DM type 2). Eighty four male subjects where included in this study and divided into three groups. Group 1, healthy controls (n=28), group 2 were patients of pulmonary tuberculosis without DM (n=28) and group three were pulmonary TB patients with newly diagnosed DM type 2 (n=28). Serum GH and fasting blood glucose levels were determined before starting anti-TB treatment in the TB patients and treatment of hyperglycemia in diabetic patients.Statistically significant difference was observed between serum GH and FBG levels of the three study groups.There was a significant difference between serum GH and FBG levels of TB patients with and without diabetes mellitus before starting anti-TB treatment. It is concluded that the hyperglycemic effects of GH on glycemic control should be taken into consideration when treating TB diabetic patients.

Keywords: Pulmonary tuberculosis, Growth hormone, Fasting blood glucose.

INTRODUCTION

World Health Organization (WHO) estimated that 1.5 million people died from TB around the world in 2013[1]. Pakistan is one of the five countries that carry almost half the world's TB burden[2].

Diabetes mellitus is a chronic disease that occurs either due to insufficient insulin production from pancreasor when the body cannot effectively use the insulin it produces.There are two types of this disease, Type 1 due to complete loss of insulin production by pancreatic beta cells [5] and Type 2 results from the body's ineffective use of insulin.[3]

Ninety percent diabetics around the world have type 2 DM[4]. Prevalence of DM in Pakistan's urban areas is 6% in males and 3.5% in females [5].

DM is found in 10-30% tuberculous patients [6,7]and studies do suggest that these two diseases are linked with each other and coexist in many patients[8].

The endocrine disturbances in tuberculosis involve raised growth hormone level [9]and up to 5-18 times higher levels were observed in such patients due to release of cytokines during an immune response to the disease that activates the hypothalamus-pituitary-adrenal axis [10].

Growth hormone is secreted from anterior pituitary gland in form of pulses throughout day and night[11]. The basal level in humans is < 0.1microgram/L [12]. It has important effects on growth and metabolism of proteins, fats and carbohydrates[13].

Previously it was reported that ATT drugs such as Rifampicin are potent hepatic enzyme inducers and lead to hyperglycemia in diabetic patients. These may stimulate clinical features of DM in previously non-diabetic patients by enhancing intestinal glucose absorption[14].

The aim of this study was to determine and compare the levels of fasting serum GH and FBG in newly diagnosed male pulmonary TB patients with and without DM type 2 before starting anti-TB treatment since these levels were yet not reported in the Pakistani population.

METHODOLOGY

This was across sectional comparative study. Subjects were selected from Lahore General Hospital and Gulab Devi Chest Hospital, Lahore for nine consecutive months.Sample size was calculated using power of the study 90% and α level of 5%. The study populationconsisted of 84 male subjects between 30-55years of age and with a normal body mass index. These were divided equally into 3 groups.Inclusion criteria for group: 1was no history of TB and DM(n=28), for Group:2newly diagnosed patients of pulmonary TB with no history of DM, Group 3newly

diagnosed patients of pulmonary TB and DM type 2 or known diabetic not getting treatment for past 1 month. Diagnosis was based on WHO criteria: Fasting blood glucose ≥7.0mmol/L (126mg/dl) or random blood glucose ≥11.1mmol/L[15]. Subjects with history of current GH or current steroid intake, hypertension, major surgical intervention in past 3 months, endocrine disorders leading to raised GH levels and extra-pulmonary TB were excluded. The Sampling technique was non-probability convenience sampling. Permission was taken from the hospitals for sample collection from the patients. Data was collected after obtaining fully informed, understood and voluntary consent of the subjects. Confidentiality of the data was ensured. Body mass index (BMI) of the patients was calculated using the following formula:

BMI = $\dfrac{\text{Weight in kilograms}^{16}}{\text{Height in meter}^2}$

Fasting Blood Glucose was measured in all the patients using a hand held glucometer (Accu-Check) based on glucose oxidase method. The patients were then instructed to come next morning at 8:00 a.m after an overnight fast of 12 hours for blood sample collection. The patients were also instructed not to do strenuous exercise and not to take a high protein diet 12 hours before coming for sampling. All samples were drawn in sitting position after a rest of at least 10-15 minutes. Five milliliter (ml) of venous blood was collected in yellow topped vaccutainers. The blood was centrifuged at 3000 revolutions per minute for 20 minutes to separate the serum for subsequent hormone analysis. The serum was divided into aliquots and stored at -80˚C.

Quantitative determination of Glucose in serum was done by a glucose oxidase kit of Pointe Scientific, Inc. USA using photoelectric colorimeter, AE-11, Tokyo Erma Optical works, LTD. Japan. Quantitative determination of fasting serum GH was done by using enzyme linked immunosorbent assay (ELISA) test kit of Bio Check, Inc. USA and ELISA analyzer Rayto RT 2100 C, USA.

STATISTICAL ANALYSIS

Statistical analysis was conducted using statistical package of social sciences (IBM SPSS 20). Fasting serum GH, FBG level and sociodemographic variables (age and socioeconomic status) were tested for significance using tests of normality (Kolmogorov-Smirnovtest).The quantitative variables of the cases were presented as median and interquartile ratio (IQR). Since the data was not normally distributed Kruskal Wallis test was used for comparison of medians of the three study groups. Mann Whitney U test was applied

for pair wise comparison of the variables. A P-value ≤ 0.05 was considered statistically significant.

RESULTS

A statistically significant difference (p=0.001) was found between the median BMI of the three study groups by applying Pearson Chi-Square test.A highly statistically significant difference was found between the fasting GH levels (p= 0.001) and the fasting blood glucose levels of the three study groups (p= 0.000) by applying Kruskal Wallis test(Table:1). A highly statistically significant difference was found between median fasting GH levels of group 1 and 2 (p= 0.001, Table:2) and group 1 and 3 (p= 0.018, Table:3) by applying Mann Whitney U test.
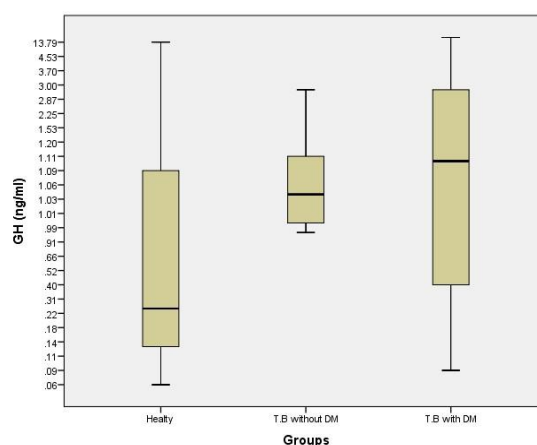

Fig. 1: Median and interquartile ratio (IQR) of serum growth hormone in the study groups.

Table 1: Comparison of serum GH and FBG between the study groups using Kruskal-Wallis test

Biochemical parameter	P-value
GH (ng/ml)	0.001*
FBG (mg/dl)	0.000*

*P ≤0.05 considered statistically significant

Table 2: Comparison of serum GH and FBG between group 1 and 2 using Mann-Whitney U test

Biochemical parameters	Group1 (n=28) Median (IQR)	Group2 (n=28) Median (IQR)	P-value
GH (ng/ml)	0.241(0.122-2.183)	1.039(0.986-1.106)	0.001*
FBG (mg/dl)	68(63.25-76.50)	75(69.25-81.75)	0.035*

A highly statistically significant difference was found between FBG levels of group 1 and 3 (p= 0.000, Table: 3), group 2 and 3 (p= 0.000, Table: 4) and group 1 and 2, (p= 0.035, Tale 2).

Table 3: Comparison of serum GH and FBG between group 1 and 3

Biochemical parameters	Group1 (n=28) Median(IQR)	Group3 (n=28) Median (IQR)	P-value
GH (ng/ml)	0.241(0.122-2.183	1.131(0.384-2.99)	0.018*
FBG (mg/dl)	68(63.25-76.50)	154(104.25-214.75)	0.000*

Table 4: Comparison of serum GH and FBG between group 2 and 3

Biochemical parameters	Group2 (n=28) Median (IQR)	Group 3 (n=28) Median (IQR)	P-value
GH (ng/ml)	1.039(0.986-1.106)	1.131(0.384-2.99)	0.974
FBG (mg/dl)	75(69.25-81.75)	154(104.25-214.75)	0.000*

DISCUSSION AND CONCLUSION

In the present study, serum GH levels were significantly different (p= 0.001) between the three study groups. The median serum GH level was highest in TB diabetic group and lowest in the healthy control group. These results are consistent with the findings of a previous study that reported that the altered immune-endocrine environment of M.TB infection, favors a significantly higher serum GH level in pulmonary TB cases as compared to healthy controls[9]. In pulmonary TB raised serum GH levels will be beneficial to contain M.TB infection in lungs since it primes macrophages for increased reactive oxygen species (ROS) production and also activates human monocytes for enhanced hydrogen peroxide release[17]. In addition, administration of GH to hypopituitary animals restores many macrophage functions relevant to infection and inflammation. The ability to release TNF-α and superoxide (O^{-2}) was increased in triggered macrophages taken from hypopituitary animals treated with GH [18]. GH mediates majority of its effects through production of IGF-1. Serum IGF-1 level was not determined in the present study since there are certain limitations to measurnment of IGF-1 in TB and DM. It has been reported that the concentration of IGF-1 is affected by under-nutrition, chronic illness and diabetes mellitus [19]. In the present study it was found that there is a statistically significant difference (p=0.035) between fasting blood glucose levels of healthy control and TB groups. GH itself is known to be a hyperglycemic hormone. Studies conducted in GH deficient adults showed that GH replacement therapy induces glucose intolerance[20]. A statistically significant difference was found between fasting blood glucose levels of TB non-diabetic patients and healthy controls. GH levels are raised in TB and TB diabetic patients as compared to healthy controls. Since GH is a hyperglycemic hormone, its effects should be considered before treating TB patients.

REFERENCES

1. World Health Organisation. Tuberculosis Fact sheet N⁰104 October 2015, [online].Available:<http://who.int/publications/fact sheet/index.htm>.
2. World Health Organization report 2009: Global tuberculosis control: surveillance, planning, financing: Geneva: world Health Organization; 2009.[online].Available:<http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf>.
3. Cantley, J. and Ashcroft, F.M., 2015. Q&A: insulin secretion and type 2 diabetes: why do β-cells fail?[online]. Available:<https://doi.org/10.1186/s12915-015-0140-6>.
4. Scully, T. 2012. Diabetes in numbers. *Nature*, **17**; 485(7398):S2-3
5. Shera, A.S., Jawad, F. and Maqsood, A., 2007. Prevalence of diabetes in Pakistan. *Diabetes. Res. Clin. Pr.,* **76**(2): 219-222.
6. Alisjahbana, B., Van Crevel, R. and Sahiratmadja, E., 2006. Diabetes mellitus is strongly associated with tuberculosis in Indonesia. *Int. J. Tuberc. Lung Dis.,* **10**: 696– 700.
7. Singla, R., Khan, N., Al Sharif, N., Ai-Sayegh, M.O., Shaikh, M.A. Osman, M.M. 2006. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. *Int. J. Tuberc. Lung Dis.*, **10**: 74–79.
8. Skowronski, M., Ziolkiewicz, D.Z. and Wojewódzki, A.B., 2014. Tuberculosis and diabetes mellitus–an underappreciated association. *Arch Med Sci.*, **10**(5): 1019–1027.

9. Del Rey, A., Mahuad, C.V., Bozza, V.V., Bouge, C., Farroni, M.A., Bay, M.L., Bottasso, O.A. and Besedovsky, H.O., 2007. Endocrine and cytokine responses in humans with pulmonary tuberculosis. *Brain Behav. Immun.,***21**: 171–179.

10. Bottasso, O., Bay, M.L., Besedovsky, H. and Del Rey, E.A., 2007. The Immunoendocrine Component in the Pathogenesis of Tuberculosis. *Scand. J. Immunol.*, **66**: 166-175.

11. Awan, T.M., Sattar, A. and Khattak, I.G., 2006. High growth hormone levels in clinically short stature children. *J. Ayub. Med. Coll.*, **18**(2): 29-33.

12. Kronenburg, H.M., Melmed, S., Polonsky, K.S. and Larsen, P.R. ed., 2008. Williams Textbook of Endocrinology. Philadelphia: Elsevier.

13. Wei, Y., Puzhko, S., Wabitsch, S. and Goodyer, C.G., 2009. Structure and Activity of the Human Growth Hormone Receptor (*hGHR*) Gene V2 Promoter. *Mol. Endocrinol.,* **23**(3): 360-372.

14. Atkin., S.L., Masson, E.A., Bodmer, C.W., Walker, B.A., White, M.C.1993. Increased insulin requirement in a patient with Type 1 diabetes on rifampicin. [online]. Availableat:<https://doi.org/10.1111/j.1464-5491.1993.tb00086.x>

15. World Health Organization: definition and diagnosis of diabetes mellitus and intermediate hyperglycemia Report of a WHO/IDF Consultation; 2006. [online].Availableat<http://www.who.int/diabetes/publications>.

16. Hall, J. E.ed., 2011. Guyton and Hall Textbook of Medical Physiology. Philadelphia: Elsevier.

17. Voskuil, M. I., Iona, L., Bartek, Visconti, K., and Schoolni, G.K., 2011. The response of Mycobacterium tuberculosis to reactive oxygen and nitrogenspecies. [online]. Available at<https://doi.org/10.3389/fmicb.2011.00105>.

18. Livingstone , C. 2012. The Insulin-Like Growth Factor System and Nutritional Assessment. [online]. Available at :<http://dx.doi.org/10.6064/2012/768731>.

18. Derek, L.D. and Yakar, S. 2007. Mechanisms of Disease: metabolic effects of growth hormone and insulin-like growth factor 1. *Nat. Clin. Pract. Endocrinol. Metab.,***3**:302–310.

19. Thissen, J., Ketelslegers, J. and Underwood, L.E., 1995. Nutritional regulation of the Insulin-like growth factors. *Endocr. Rev*.,**15**(1): 80-101.

20. Kim, S. and Park, M. 2017. Effects of growth hormone on glucose metabolism and insulin resistance in human. *Ann. Pediatr. Endocrinol. Metab.,* **22**(3):145-152.