Sluggish glucose tolerance in tuberculosis patients

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Objective. To examine glucose tolerance in sputum-positive non-treated pulmonary tuberculosis (TB) patients as part of a general metabolic profile.

Subjects. Sixty-three sputum-positive non-treated patients (male and female) attending the pulmonary clinic at Mthatha General Hospital in the Eastern Cape and 89 apparently healthy sex- and age-matched volunteers.

Methods. Sixty-three untreated TB patients who came to the Mthatha General Hospital's pulmonary clinic with classic symptoms of TB, confirmed by sputum analysis, were recruited for the study. Eighty-nine apparently healthy sex- and age-matched volunteers served as the control group. Anthropometric measurements were taken using an electronic scale. Standard oral glucose tolerance tests (OGTTs) were performed in both groups in the morning after an overnight fast. Anticoagulant-treated blood was analysed for glucose and insulin using Peridochrome Glucose (Boehringer Mannheim, Mannheim, Germany) and radioimmunoassay (RIA) (Diagnostic Products Corporation, Los Angeles, USA) respectively.

Results. There was sluggish response to glucose and insulin in the TB patient group compared with the control group. Glucose and insulin levels were significantly higher in patients at 0, 30, 60, 120, and 180 minutes. Analysis of variance gave the following *p*-values, viz. $p = 0.0000, 0.0004, 0.0000, 0.0000$ and 0.0000 for glucose, and $p = 0.0317, 0.0071, 0.0000, 0.0005$ and 0.0000 for insulin respectively.

Conclusions. The results of this study suggest an altered glucose/insulin metabolism in TB patients. This might play an important role in the clinical course of the disease.

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It is accepted that individual susceptibility plays an important aetiopathogenic role in tuberculosis (TB) depending on the immunological strength of the person infected by *Mycobacterium tuberculosis*.[1] The susceptibility might be genetic, acquired or both, but it is always expressed in the metabolism of the individual. The wasting syndrome present in many TB patients suggests an impaired insulin/glucose metabolism on the basis that insulin is a hormone of universal action, the main growth factor in the human body, and glucose qualitatively the main fuel.[2]

Various experimental methods and modelling approaches have been developed to assess the metabolism of insulin and glucose in humans.[3] The oral glucose tolerance test (OGTT) is a very useful tool because of its simplicity and the reliability of the physiological and biochemical characteristics of the patient. Although the abovementioned modelling relates mainly to the diagnosis and assessment of diabetes, impaired insulin/glucose metabolism may occur in other pathological states too, and the same methodology can be applied to assess the insulin/glucose profile in these cases. Borderline diabetes has been reported in TB cases[4] and diabetes has also been considered a risk factor for TB.[5] Some other metabolic derangements have also been reported in TB.[6] The question is whether the metabolic derangements are part of the clinical course of the disease, or whether people with these types of metabolic derangements are prone to TB.

It is well known that only 5 - 6% of people infected with *M. tuberculosis* develop the disease,[7] which is clear evidence that individual susceptibility plays an important role in the aetiopathogenesis of TB. It is not clear which part of the defence system is damaged or weakened in those people. The relationship between impaired cellular immunology and impaired insulin function has also been reported.[8,9] This article reports on a study of the OGTT in untreated TB patients compared with a matched control group.

Material and methods

Sixty-three untreated TB patients were recruited from the Mthatha General Hospital pulmonary clinic; these patients came to the clinic with the classic symptoms of TB and the condition was confirmed by sputum analysis. The subjects were studied and compared with 89 apparently healthy sex- and age-matched volunteers as the control population. Height and weight were determined using an electronic scale. Standard OGTTs were performed in both groups in the morning (07h00 - 08h00) after an overnight fast. Blood samples were taken from the antecuvital vein in a vacutainer with sodium fluoride/potassium oxalate as anticoagulant

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(Vacutainer System, Becton Dickinson, Plymouth, UK) following the aseptic rules at 0, 30, 60, 120 and 180 minutes. Glucose levels in plasma were determined within 3 hours. Plasma for insulin testing was kept frozen (- 20°C) until analysed. Seventy-five grams of glucose dissolved in 300 ml drinking water were given orally to each patient and to controls. Glucose was determined colorimetrically (Peridochrome Glucose, Boehringer Mannheim) using a Photometer 5010. Insulin level was determined by radioimmunoassay (RIA) (Coat-A-Count Insulin Diagnostic Products Corporation, Los Angeles, USA). Multivalent Control Module CONS6 was used as an external explorer sample. Data were analysed with Statistica-5, applying non-parametric methods whenever necessary. Patients were tested for HIV (IMX Abbott Diagnostic Division, Wiesbaden, Germany) with the patients' consent.

Results

Results of the OGTT and insulin tests for patients and controls are presented in Figs 1 and 2. Glucose and insulin levels were found to be higher in patients than controls. Glucose peak was delayed for patients compared with controls. Further, it can be seen that glucose did not return to basal level in the patient group compared with controls. This was statistically significant for all 5 sampling times in a point-to-point analysis of variance (ANOVA) (breakdown and one-way ANOVA, $p = 0.0000, 0.0000, 0.0000, 0.0000, 0.000$). With regard to insulin (Fig. 2) the pattern was more or less similar, with a delayed peak compared with controls and non-return to basal level in a point-to-point ANOVA (Kruskal-Wallis ANOVA median test, $p = 0.0317, 0.0071, 0.0005, 0.0000, 0.0000$). As expected, basal glucose distribution was normal and insulin log-normal (Fig. 3). The correlation between glucose and log-insulin was essentially different between TB patients and controls. As expected, in the normal population there was no correlation between plasma glucose and plasma log-insulin, while the figure was totally different in the patient group (Tables I and II). There was a positive correlation between these two metabolites (glucose/log-insulin). This might be an indication that these patients were in a critical metabolic state. Thirty-two per cent of patients were confirmed HIV-positive and there was no significant statistical difference in any of the parameters between HIV-positive and negative patients. There was a significant difference in body mass index (BMI) values, viz. 19.58 and 23.80 for patients and controls respectively ($p = 0.0000$, analysis of variance, breakdown and one-way ANOVA).

Discussion

The results obtained clearly show a sluggish OGTT for both glucose and insulin suggesting a partial glucose intolerance and also the possibility of a certain insulin dysfunction in the patient group compared with the control group. The normal

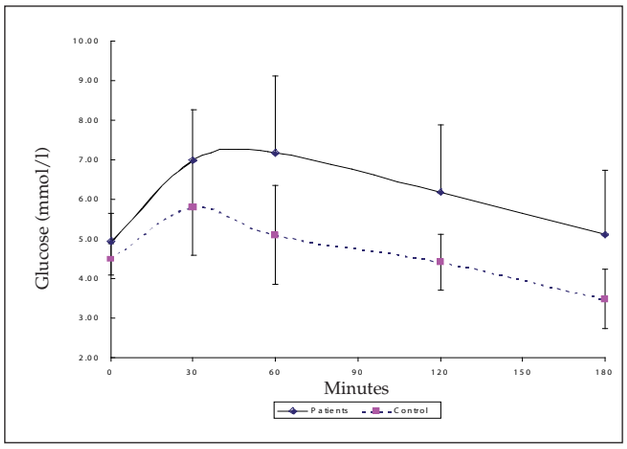

Fig. 1. Point-to-point analysis of variance (breakdown and one-way ANOVA) of glucose level (mean ± standard deviation (SD)) between untreated TB patients and the control group (p = 0.000, 0.000, 0.000, 0.000 and 0.0000) respectively for 0, 30, 60, 120 and 180 minutes.

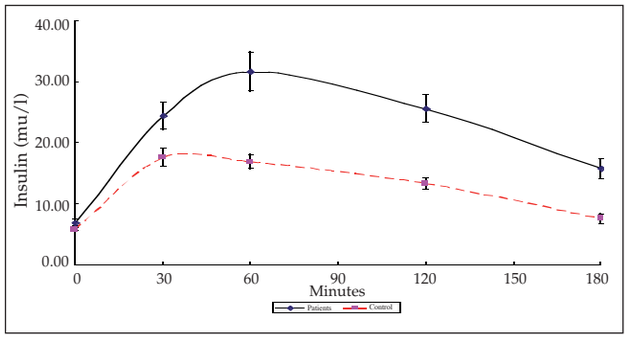

Fig. 2. Point-to-point analysis of variance (Kruskal-Wallis ANOVA median test) of insulin level (mean ± standard error (SE)) between untreated TB patients and the control group (p = 0.0317, 0.0071, 0.005, 0.0000 and 0.0000) respectively for 0, 30, 60, 120 and 180 minutes.

OGTT is based on the absorption of glucose, which should peak in blood at 20 - 40 minutes, returning to basal level at 90 minutes.[6] Insulin secretion is triggered by increased level of glucose in blood plus some other intestinal factors.[10] The insulin level should peak in blood at 30 - 40 minutes and should return to basal level at 180 minutes. Anything different from this pattern tends to be associated with pathological events. A flat pattern expresses improper intestinal-pancreatic physiology or diabetic-like state due to improper glucose and insulin uptake by the peripheral tissues. It has been established that a value above 7.8 mmol/l or 11.1 mmol/l of blood glucose at 120 minutes after oral glucose load is considered intolerant or diabetic.[11] But between 'diabetic' or 'intolerant' and normal there is a gap, which looks to be associated with several pathological states (silent killer).[12]

Glucose has been evolutionally selected as the main fuel for all type of cells; without it there is no proper biology in humans. Insulin, on the other hand, has been selected as the main growth factor in the body.[2,13] Unfortunately for most

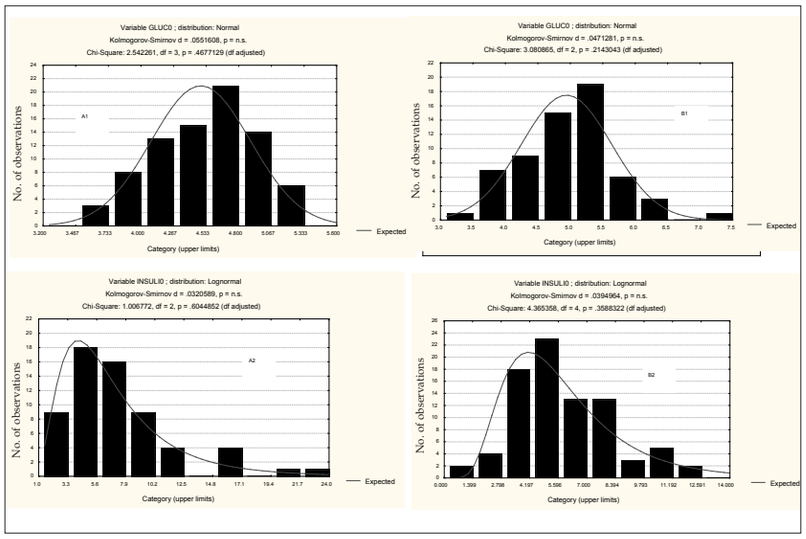

Fig. 3. Distribution of fasting glucose (normal) and insulin (log-normal) (A1= glucose; A2 = insulin (patient); B1 = glucose; B2 = insulin (control)).

people its only role is the glucose uptake by the tissues, but the main role of insulin is intracellular with non-genomic or genomic actions.[14,15] The half-life of insulin in plasma in humans is 6 - 8 minutes.[16] As such the delayed clearance of insulin in blood that we observed in the TB group suggests an impaired insulin internalisation or insulin resistance, which causes an improper intracellular action of this hormone. Furthermore the positive correlation between glucose level in plasma and log-insulin in plasma suggests that those patients are in a critical metabolic state. In any normal population there is usually no correlation between fasting insulin and fasting glucose levels in plasma, but if any correlation is expected according to the insulin mechanism of action, it should be a negative correlation, more insulin less glucose in plasma or more glucose less insulin. This positive correlation is another suggestion that those patients are in an insulin resistance state.

The relation between insulin action and the immunological mechanism of macrophages and lymphocytes has been well documented. It has been reported that insulin exerts a very strong effect on macrophage action by increasing pyruvate dehydrogenase (PDH) complex activity and some other enzymes that play an important role in their phagocyte capacity.[17] The same has also been found with regard to lymphocytes.[18,19] The mechanism of TB infection and the difference between normal persons and those prone to developing TB depend precisely on the improper function of macrophages, lymphocytes or both.[20] In a normal person infected with *M. tuberculosis*, macrophages and phagocytes are initially unable to destroy the bacteria. After some time sensitised lymphocytes attract and activate macrophages, which acquire a greatly enhanced phagocyte and destructive capability, destroying most of the micro-organism and forming the characteristic micro-granuloma. In this way the infection is arrested.[20] The difference between being susceptible to TB or not probably depends on proper lymphocyte sensitisation/ macrophage activation.

The factors regulating this immunological process should also be the target of therapeutic action in TB cases. It seems that insulin and glucose metabolism might play an important role in the process of lymphocyte sensitisation and macrophage activation. If the glucose-insulin metabolism is altered it can be expected that lymphocyte and macrophage function will also be altered, allowing the pathological course of TB. Unfortunately most therapeutic TB interventions are directed against the biology of the bacteria, with very little currently being done to restore host biology.

Table I. Correlation coefficient (*r*) between glucose and log-insulin during the OGTT

Variable	Log-insulin 0	Log-insulin 30	Log-insulin 60	Log-insulin 120	Log-insulin 180
Control group					
Glu0	-0.13	0.10	0.13	0.01	-0.13
Glu30	-0.14	0.04	0.09	0.07	0.04
Glu60	-0.13	-0.01	0.06	0.08	-0.14
Glu120	-0.11	-0.27*	0.06	0.16	-0.11
Glu180	0.08	-0.23	0.04	-0.05	0.07
TB patients					
Glu0	0.50*	0.16	0.08	0.25	0.27*
Glu30	0.14	0.33*	0.35*	0.39*	0.19
Glu60	-0.04	0.08	0.30*	0.43*	0.29*
Glu120	-0.10	-0.02	0.08	0.29*	0.33*
Glu180	-0.03	-0.20	-0.12	0.12	0.49*

* Statistical significance at least $p < 0.05$.
Glu = glucose.

Table II. Descriptive statistics for glucose and insulin at different points during the OGTT

	Mean	Standard deviation	Standard error
TB patients			
Glu0	4.94148	0.69577	0.089085
Glu30	6.98233	1.28118	0.165400
Glu60	7.17017	1.92479	0.248490
Glu120	6.17705	1.69297	0.216762
Glu180	5.11131	1.61673	0.207001
Insu0	6.95377	4.11277	0.526586
Insu30	24.43700	17.11464	2.209491
Insu60	31.64783	25.44571	3.285027
Insu120	25.63600	18.28743	2.360897
Insu180	15.83131	12.88091	1.649232
Controls			
Glu0	4.48975	0.40679	0.045480
Glu30	5.79064	1.20409	0.136337
Glu60	5.09532	1.24968	0.142414
Glu120	4.41152	0.69346	0.078021
Glu180	3.46987	0.75367	0.085336
Insu0	5.75789	2.45801	0.269801
Insu30	17.55458	13.64728	1.497983
Insu60	16.86220	10.69280	1.180823
Insu120	13.31384	9.35090	1.032634
Insu180	7.55031	7.50920	0.839554

Glu = glucose; Insu = insulin.

The results of the present study strongly suggest that insulin-glucose metabolism is altered in TB patients. It has also been reported that a diabetic-like state is present in TB patients.[4] On the other hand impaired glucose tolerance secondary to TB has also been reported.[21] The immediate question is whether this metabolic derangement is characteristic of TB pathophysiology, or whether people with this derangement are prone to TB. We believe that according to the aetiopathogenesis of the disease in which a poor immune response in the host plays an important role, the most logical explanation is that people with this derangement are prone to TB. Most importantly, in the battle against TB and increasing multidrug resistance the philosophy of solving this metabolic derangement should be introduced in the hope that it might improve host immunological strength, favouring the patients' total cure and offering less chance of multi-drug resistance.

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