Original article

STUDY OF QT_C INTERVAL IN NONDIABETIC SUBJECTS WITH IMPAIRED FASTING SERUM GLUCOSE AND HYPERINSULINEMIA

Dr. Komal K. Makwana [1] Assistant Prof **, Dr. Mukesh Dinkar** [2] Professor**, Dr. Hemant Mehta**[3]

Professor(GMC Bhavnagar)
Department of Physiology, GMERS medical college Vadnagar,
Correspondence author Dr. Mukesh Dinkar Professor & Head. Department of Physiology, GMERS medical college Vadnagar.

ABSTRACT

INTRODUCTION: India leads the world with the largest number of diabetic subjects (nearly 40 million) and it is predicted that this number would reach almost 80 million by the year 2030. There are research works those indicate towards the genetic liability of Indians towards the insulin resistance, diabetes & obesity. The constellation of insulin resistance, impaired glucose tolerance, atherogenic dyslipidaemia, hypertension and intra-abdominal adiposity (IAA) is called metabolic syndrome. This all factors contribute to high cardiovascular risk, morbidity & mortality in population. Identification of cardiovascular risk in nondiabetic subjects at early stage might be a game changer.

OBJECTIVE: The aims of our study were to evaluate the prevalence of QTc prolongation in nondiabetic subjects with impaired fasting serum glucose and hyperinsulinemia & identify the subjects with cardiovascular risks at early stage.

METHOD: We estimated fasting serum glucose & insulin in multiple subjects till we found 50 nondiabetic subjects with impaired fasting serum glucose and hyperinsulinemia. For each case we matched 50 control without insulin resistance. Subjects' heart beats were recorded on the resting ECG tracing. QTc was calculated according to Bazett's formula. Insulin Resistance& hyperinsulinemia was defined as homeostasis model assessment of IR (HOMA-IR).

RESULTS: We observed that there was significant difference in QTc interval between case & control group.

CONCLUSION: This study has concluded that Insulin resistance, estimated by HOMA-IR, was strongly correlated with prolonged QTc. Prolonged QTc identifies metabolic syndrome patients with an elevated risk of cardiovascular events.

KEY WORDS: hyper insulinemia Insulin Resistance, QTc, HOMA-IR, metabolic syndrome ,

cardiovascular risk

INTRODUCTION:

According to the recent projections of World Health Organization (WHO), India already leads the world with the largest number of diabetic subjects (nearly 40 million) and it is predicted that this number would reach almost 80 million by the year 2030.[1] Number of people with diabetes in India currently are 40.9 million is on rise to 69.9 million by 2025 unless precautions are taken. India & china have 75% of total diabetic population of world. India faces a grave health care burden due to the high prevalence of metabolic syndrome patients and its complication like cardiovascular disease. [1,2] This study about the insulin resistance & metabolic syndrome related to prolonged QTc interval, . Insulin resistance occurs when cells in the body (adipose tissue skeletal muscle and liver) become less sensitive and eventually resistant to insulin. Glucose can no longer be taken by the cells but blood, triggering hyperinsulinemia; this over burdens the pancreatic beta cell of pancreas &eventually wears out the beta cells. This is the point where clinical diabetes develops. But at this stage the cardiovascular pathogenesis like atherogenesis, hypertension already gets hold. In this study we want to identify cardiovascular risk at early stage in non diabetic patient who is only insulin resistant & has chance of reversal.

MATERIALS AND METHODS

This study was started with the permission of IRB committee & conducted in physiology department of government medical college Bhavnagar. Multiple study subjects were chosen from Bhavnagar city till we found 50 nondiabetic subjects with impaired fasting serum glucose and hyperinsulinemia & considered this one as case group. We have decided the sample size using software Raosoft with the help of prevalence rate of previous studies done in insulin resistance. We have matched each case with control that is non insulin resistant.The major criterion for selection of subject was central obesity.(Waist Circumference (WC)>/= 80Cm for female and WC>/=90Cm for male which is ethnic specific value for Indians). This criterion was based on international diabetes federation's definition of metabolic syndrome. Exclusion criteria for participation in the study will be those who had unstable weight over the past 12 weeks, a significant chronic disease or were taking medications (anti-obesity & anti hypertensive medications, steroids, thyroid hormone, anxiolytics, oral contraceptives, beta-blockers). Informed consent was taken from every participant before enrolling them for study. We had proper approach towards the subjects & given them all information regarding advantages & disadvantages of participating in study. We had established Proper history taking & examination for assessing all the cardiovascular risk factor like past history of smoking, alcoholism or family history of diabetes & hypertension etc. The measurement of fasting serum insulin & fasting glucose is essential for the study. The fasting blood sample was

taken in the morning after an overnight fast of at least 12 hour measurement of fasting insulin, fasting glucose, All the biochemical parameters were assessed in biochemistry laboratory of sir takhtasinhaji hospital of Bhavnagar which is NABL accredited. Insulin resistance will be assessed using the homeostasis model assessment (HOMA-IR). [3,4] HOMA - IR was calculated using the following formula: HOMA-IR (mmol/L _ _U/ml) is equal to fasting glucose (mmol/L) multiplied by fasting insulin (IU/ml)/22.5. Based on the number of insulin resistance, subjects were divided in 2 groups insulin resistant (greater than 3.04) & insulin sensitive. (less than or equal to 3.04).All the blood samples are collected from the individual in fasting blood samples without anticoagulant and centrifuge at 1500 rpm for 5 min and serum is collected in fresh vial for biochemical studies by using standard methods as follows. Fasting plasma insulin level (Ins)was determined using an immunoenzymatic method(analyzer AXSYM, Abbott) and fasting glucoseconcentration by the glucose oxidase method. FastingInsulin, the fasting Glucose /Insulin ratio and the homeostasisassessment model for insulin resistance (HOMA-IR= fasting Ins (mU/l) * fasting Glucose (mmol/l)/ 22.5) were chosen as measures of insulin sensitivity. [5,6]

QT intervals and the preceding RR intervals were measured on the resting ECG tracing in lead II. The QT interval was measured manually from the starting point of QRS complex to the terminal point of the down slope of the T wave. QTc was calculated according to Bazett's formula QTc=QT/(RR)1/2. The QTc interval >0.44s was considered abnormally prolonged.

OBSERVATION AND RESULTS

Statistical tools: Data were entered and analysed with the Graph Pad.com. Statistical tests used for comparison is Student's t-test. Results are presented as mean (SD) and number (%) of cases as appropriate. The level of significance was set at $P < 0.05$, and 95% confidence intervals were calculated for the main outcome measures.

TABLE 1 distribution of subjects

Insulin sensitivity index	No. of subjects
Insulin sensitive(≤ 3.04) controls	50
Insulin resistant(> 3.04) case	50

Figure-1 Fibroadenoma (H&E stain) Figure- 2 Fibrocystic disease(Giemsa stain)

TABLE 2 comparison of HOMA IR in case & controls(unpaired t test)

Groups	Mean ± SD	T value	P value
case	5.11±1.89	<6.603	<0.0001

control	2.42±0.74		

TABLE 3 comparison of QTc interval in case & controls(unpaired t test)

Groups	Mean ± SD	T value	P value
case	0.3868±0.7993	<4.004	<0.05
control	0.3028±0.0679		

DISCUSSION

In our study QTc interval is an index of myocardial refractoriness and electrical stability. Its prolongation was associated with ventricular morbidities and cardiac sudden death [7]

A significant positive correlation between QTc interval and HOMA IR level was also found in our study. This finding is same as the findings of Kazumi et al. [8] & Takebayashi et al. [9], insulin therapy was also demonstrated to significantly increase QTc interval[10], as compared with the standard-therapy group.

In some studies, a prolonged QTc interval has been associated with aging, female sex, arterial hypertension (mainly systolic blood pressure), underlying coronary artery disease we have studies indicating A significant positive correlation between QTc and fasting insulin level was also found in our study. This finding is same with Kazumi et al. Diabetes and impaired glucose tolerance have been related to QTc prolongation, probably as part of the insulin resistance syndrome resulting from increased sympathetic activity or impaired glucose use at myocardial cells . [11,12,13,14]

Stimulation of cellular potassium uptake is insulin-induced which leads to hyperpolarization [15]. Hyperpolarization prolongs the repolarization phase by dispersion of action potential recovery which leads to prolongation of QT interval. Insulin also leads to Hypokalemia. Which could mediate adrenergic and sympathetic overactivity resulting in prolongation of QTc interval., van Noord et al. showed that the prolongation of QTc interval is due to shortening of RR interval associated with hyperinsulinemia in nondiabetic [16]

Thus ,prolongation of QTc interval may be one of the factors contributing to the high rate of death in the intensity-therapy group. From all of above it seems like Indians are high risk subject for metabolic syndrome & cardiovascular morbidity. To decrease the global burden of syndrome X, we must focus our preventive guideline to high risk group which is insulin resistant group.

CONCLUSION AND SUMMARY

the current study has shown that the prevalence of prolonged QTc interval among nondiabetic subjects with impaired fasting serum glucose and hyperinsulinemia is considerably high. metabolic syndrome is a risk factor for prolonged QTcs, which may further increase cardiovascular morbidity and mortality in the subjects with metabolic syndrome.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27 : 1047-53. Yong WS, Chia KH, Poh WT and Wong CY. A comparison of trucut biopsy with fine needle aspiration cytology in the diagnosis of breast cancer. Singapore Med J. 1999; 40(9): 1-2.
2. Alberti KG, Zimmet P, Shaw J. IDF Epidemiology Task 4. Force Consensus Group: The metabolic syndrome—a new worldwide definition. Lancet 2005; 366: 1059-62.
3. Kayo S, Tetsuo S. Insulin Resistance as an Independent Predictor of Cardiovascular Mortality in Patients with End-Stage Renal Disease. Journal of the American Society of Nephrology 2002 ;13: 1894–1900,Pouliot MC, Després JP, Nadeau A, Moorjani S, Prud'Homme 6. D, Lupien PJ, et al. Visceral obesity in men. Associations with glucose tolerance, plasma insulin and lipoprotein levels. Diabetes 1992; 41 : 826 -34.
4. Kayoung L. Usefulness of the metabolic syndrome criteria as predictors of insulin resistance among obese Korean women journal of Public Health Nutrition2009;13:181–186
5. Eleni N, Serum adiponectin levels, insulin resistance, and lipid profile in children born small for gestational age are affected by the severity of growth retardation at birth. European Journal of Endocrinology; 2007: 271–277
6. Mohan V, Sharp PS, Cloke HR, et al. Serum immunoreactive insulin responses to a glucose load in Asian Indian and European Type 2 (non insulindependent) diabetic patientsand control subjects. Diabetologia 1986;29:235-7.
7. A. Fiorentini, A. Perciaccante, R. Valente, A. Paris, P. Serra, and L. Tubani, "The correlation among QTc interval, hyperglycaemia and the impaired autonomic activity," Autonomic Neuroscience, vol. 154, no. 1-2, pp. 94–98, 2010.
8. T.Kazumi,A.Kawaguchi,J.I.Katoh,Y.Ikeda,K.Kishi,andG. Yoshino, "Fasting serum insulin concentrations are associated withQTcdurationindependentofserumleptin,percentbody fat, and BMI," Diabetes Care, vol. 22, no. 11, pp. 1917–1918, 1999.
9. K. Takebayashi, R. Naruse, K. Morita, Y. Aso, and T. Inukai, "The effect of insulin therapy and plasma glucose levels on corrected QT intervals in patients with type 2 diabetes," JournalofClinicalMedicineandResearch,vol.4,pp.1–5,2012.
10. H. C. Gerstein, M. E. Miller, R. P. Byington et al., "Effects of intensive glucose lowering in type 2 diabetes," The New England Journal of Medicine, vol. 358, no. 24, pp. 2545–2559, 2008.
11. Rautaharju PM, Manolio TA, Psaty BM, Borhani NO, Furberg CD, for the Cardiovascular Health Study Collaborative Research Group. Correlates of QT prolongation in older adults (the Cardiovascular Health Study). Am J Cardiol. 1994;73:999–1002.
12. Festa A, D'Agostino R Jr, Rautaharju P, Mykkänen L, Haffner SM. Relation of systemic blood pressure, left ventricular mass, insulin sensitivity, and coronary artery disease to QT interval duration in nondiabetic and type 2 diabetic subjects. Am J Cardiol. 2000;86:1117–1122.

13. Dekker JM, Feskens EJ, Schouten EG, Klootwijk P, Pool J, Kromhout D. QTc duration is associated with levels of insulin and glucose tolerance: the Zutphen Elderly Study. Diabetes. 1996;45:376–380
14. Brown DW, Giles WH, Greenlund KJ, Valdez R, Croft JB. Impaired fasting glucose, diabetes mellitus and cardiovascular disease risk factors are associated with prolonged QTc duration: results from the Third National Health and Nutrition Examination Survey. J Cardiovasc Risk. 2001;8:227–233
15. A. Gastaldelli, M. Emdin, F. Conforti, S. Camastra, and E. Ferrannini, “Insulin prolongs the QTc interval in humans,” American Journal of Physiology—Regulatory Integrative and Comparative Physiology, vol. 279, no. 6, pp. R2022–R2025, 2000.
16. C. van Noord, M. C. J. M. Sturkenboom, S. M. J. M. Straus et al., “Serum glucose and insulin are associated with QTc and RR intervals in nondiabetic elderly,” European Journal of Endocrinology, vol. 162, no. 2, pp. 241–248, 2010.