

2016 sl/ ①

SERUM INSULIN LEVELS – IS IT A GOOD INDICATOR IN CHRONIC TYPE-2 DIABETES MELLITUS SUBJECTS?

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Introduction

Type 2 diabetes (T2D) is characterized by hyperglycaemia due to defects in secretion of insulin and its action. Insulin resistance (IR) and hyperinsulinaemia are considered as key features of T2D. Worldwide prevalence of T2D has been increasing significantly. About 347 million people worldwide have diabetes and 90 % of them have T2D. South East Asian region accounts for the 2nd highest number of T2D cases and in Sri Lanka prevalence of diabetes was 10.3 % in 2008. The IR is a condition where insulin levels are higher than expected and also relatively higher to the level of glucose in the blood. Therefore hyperinsulinaemia is often caused by IR where genetic and environmental factors influence hyper secretion of insulin hormone from β -cells which ultimately leads to hyperinsulinemia. IR is the major underlying causative factor of metabolic syndrome (MS) and is one of the risk factors for several non-communicable diseases (NCD) such as type 2 diabetes, dyslipidaemia and cardiovascular diseases (CVD).

Several studies have introduced IR as a powerful predictor of T2D. Fasting serum insulin (FSI) level of normal healthy subjects in Sri Lanka was, 93.42 ± 54.17 (21.53-376.42) pmol L⁻¹, while FSI among Sri Lankan diabetics was 150.71 ± 87.37 (41.67-390.31) pmol L⁻¹ (Senevirathne et al. 2009). IR in urban and rural adult population in Sri Lanka was 22.3 %. T2D is linked with basal hyperinsulinaemia, reduced sensitivity to insulin, and disturbances in insulin release. Even though FSI is currently being measured in diabetes subjects some studies state that chronic T2D subjects with FPG exceeding 7.8 mmol L⁻¹ secrete insulin levels at a low level which is similar to healthy non-diabetic individual or even lower. Therefore in chronic diabetics, basal insulin secretion and FSI can be within the normal range or even lower. Even though studies have indicated serum insulin level as a marker of IR. Eventually, C-peptide has gained attention as an alternative marker for IR, which is a protein that is co-secreted with insulin on an equimolar basis from pancreatic beta cells. Unlike insulin, it doesn't undergo hepatic first pass metabolism, has a longer half-life, and has been recognized as a more stable and accurate marker of endogenous insulin secretion and the pancreatic health.

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Hence this study was carried out to identify insulin resistance, hyperinsulinaemia and its association with FPG in a selected Sri Lankan T2D population and also to assess the clinical relevance of FSI in chronic diabetes subjects.

Materials and Methods

Diabetic subjects (121) aged 27-80 years who were already diagnosed as having diabetes mellitus by a registered medical practitioner or government hospitals and attend the clinic at Family Practice Centre, Faculty of Medical Sciences, University of Sri Jayewardenepura were enrolled, after obtaining ethical approval from the Ethics Review Committee of USJP. Informed written consent was obtained prior to the study. An interviewer administered questionnaire was used to collect information about socio-demographic factors, family history of diabetes, lifestyle patterns and physical activity.

About 3 mL of 8 - 10 hours overnight fasting venous blood samples were obtained from each subject to analyze FPG and FSI. Glucose oxidase method was used to measure plasma glucose level and solid phase Enzyme-Linked Immunosorbent Assay (ELISA) method was used for serum insulin assay. IR was estimated by the HOMA-IR, using the equation $HOMA-IR = [FSI (\mu U mL^{-1}) \times FPG (mmol L^{-1})] / 22.5$ (Schianca et al. 2003). FPG level was classified based on World Health Organization criteria [WHO, 2006]. Hyperinsulinaemia was measured when FSI is $\geq 75^{th}$ percentile of its distribution (Freiberg et al. 2004). As a measure of IR, subjects having $HOMA-IR \geq 2.6$ was taken as insulin resistant (Schianca et al. 2003). Results were analyzed using SPSS version 16 and Microsoft Excel 2010. Correlations and significant differences were determined and $p < 0.05$ was considered as significant.

Results and Discussion

Among the 121 study subjects, 64.5 % ($n = 78$) were females. Mean age of the study population was 59 ± 11 years. Most of the subjects were residing in Colombo (66.9 %) and majority had a monthly income $< Rs. 20000$ (72.7 %). Majority of the study population (62.8 %) had diabetes ≥ 5 years. Among the study population, 58.7 % had a family history of diabetes. Those who had $FPG \geq 7 mmol L^{-1}$ ($n=59$), 66.1 % had a known family history for diabetes. These findings were supported by several prospective studies where first-degree family history had a strong correlation with twofold increased risk of future T2D. This denotes that genetic predisposition is a risk factor in development of T2D and those with family history should have proper screening time to time and ones who are already diagnosed should have a proper follow up and monitoring.

Study subjects had an average FPG value of $8.0 \pm 3.45 \text{ mmol L}^{-1}$ which indicates a poor glycaemic control among the subjects. Large number of the study population (82.7 %) had FPG value above the normal range ($\geq 4.0\text{-}5.6 \text{ mmol L}^{-1}$) suggestive of poor glycaemic control among the subjects. In this study population, good percentage (56.2 %) of subjects monitors FPG levels monthly. Blood glucose monitoring at least once in every 3 months would enable to see the effect of treatment and aids in assessing the patients' compliance. It is recommended that subjects with high risk and those who have complications should monitor their FPG levels at least every 3 months.

Geometric mean of FSI among the subjects was $34.67 \pm 2.3 \text{ pmol L}^{-1}$ which was below the given normal FSI value for normoglycaemic subjects (Senevirathne et al. 2009). Among the hyperinsulinaemic subjects geometric mean of FSI was $89.12 \pm 2.3 \text{ pmol L}^{-1}$. Though mean FSI of these subjects were within the normal range ($18\text{-}172 \text{ pmol L}^{-1}$) (Sultan et al. 2010) mean FSI of hyperinsulinaemic subjects was lesser than the given mean FSI for diabetics. Subjects whose FPG was $\geq 7 \text{ mmol L}^{-1}$, had a mean serum insulin level of $39.8 \pm 1.8 \text{ pmol L}^{-1}$ which indicates that FSI is normal in these T2D subjects. Concerning the duration of having diabetes among the T2D subjects even with high FPG, both groups with the duration less than and greater than 5 years had (less) geometric mean of insulin levels but similar in both groups (FPG 8.3 and 7.8 mmol L^{-1} and insulin 33.1 and 36.3). This may be due to deterioration of beta cells and are unable to maintain insulin secretion hence FSI decline precipitously. Yet 38 % of the study subjects were insulin resistant according to HOMA-IR values and their mean FPG and FSI levels were $9.7 \pm 4.3 \text{ mmol L}^{-1}$ and $69.18 \pm 1.58 \text{ pmol L}^{-1}$, respectively. Out of the subjects who had FPG $\geq 7 \text{ mmol L}^{-1}$, 54.2 % had HOMA-IR ≥ 2.6 but only 20.3 % of them had hyperinsulinaemia. Further FPG and FSI had a significant positive correlation with IR ($p=0.000$). Significantly higher mean FPG levels ($p<0.05$) were observed with insulin resistant subjects (HOMA-IR ≥ 2.6) and lesser frequency of screening ($<$ monthly) for FPG. Despite monthly income $\geq \text{Rs. } 20\,000$, lesser frequency of screening was observed in these study subjects and also they had FSI & HOMA-IR ≥ 2.6 which was significantly higher ($p<0.05$).

These findings were supported by American Diabetes Association (2010), indicating that T2D is strongly linked with insulin resistance but diabetics are not necessarily to become hyperinsulinaemic. Thus chronic T2D subjects can present with normal FSI hence low FSI in chronic diabetics is not an indicator of good control. Yet, hyperinsulinaemia can be a strong predictor of development of T2D and metabolic syndrome.

Conclusions and Recommendations

Though it is assumed that poorly controlled chronic diabetic subjects have high FSI, this study demonstrates that, FSI is not a good indicator to assess glycaemic control in chronic T2D subjects. FPG and FSI have a significant correlation with IR. Furthermore, frequency of screening of FPG levels and first degree family history plays a major role in the FPG levels in T2D subjects. Therefore it is recommended to increase the FPG screening frequency at least once in 3 months in subjects with a known family history and not to assess the FSI values in chronic T2D.

Acknowledgement

Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura for financial support & laboratory assistance. Dr. W.A.A. Wijesiri, Department of Community Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura for the statistical advice. Ms. Kasuni Walatara, for the guidance and advices on statistical analysis and for the assistance during the project. Medical and laboratory staff of the Family Practice Centre for their assistance during sample collection.

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