Fasting Insulin is Better Partitioned according to Family History of Type 2 Diabetes Mellitus than Post Glucose Load Insulin of Oral Glucose Tolerance Test in Young Adults

SARITHA FRANCIS[1], SINDHU PADINJAREVEEDU CHANDRAN[2], NESHEERA KK[3], JOSE JACOB[4]

ABSTRACT

Introduction: Hyperinsulinemia is contributed by insulin resistance, hepatic insulin uptake, insulin secretion and rate of insulin degradation. Family history of type 2 diabetes mellitus has been reported to cause hyperinsulinemia.

Aim: Correlation of fasting insulin with post glucose load Oral Glucose Tolerance Test (OGTT) insulin in young adults and their partitioning according to family history of type 2 diabetes.

Materials and Methods: In this observational cross-sectional study, clinical evaluation and biochemical assays of insulin and diabetes related parameters, and secondary clinical influences on type 2 diabetes in volunteers were done for inclusion as participants (n=90) or their exclusion. Cut off levels of quantitative biochemical variables were fixed such that they included the effects of insulin resistance, but excluded other secondary clinical influences. Distribution was analysed by Shapiro-Wilk test; equality of variances by Levene's test; Log_{10} transformations for conversion of groups to Gaussian distribution and for equality of variances in the groups compared. When the groups compared had Gaussian distribution and there was equality of variance, parametric methods were used. Otherwise, non parametric methods were used.

Results: Fasting insulin was correlating significantly with 30, 60 and 120 minute OGTT insulin showing that hyperinsulinemia in the fasting state was related to hyperinsulinemia in the post glucose load states. When fasting and post glucose load OGTT insulin were partitioned into those without and with family history of type 2 diabetes, maximum difference was seen in fasting insulin (p<0.001), followed by 120 (p=0.001) and 60 (p= 0.002) minute OGTT insulin. The 30 minute insulin could not be partitioned (p=0.574).

Conclusion: Fasting, 60 and 120 minute OGTT insulin can be partitioned according to family history of type 2 diabetes, demonstrating stratification and heterogeneity in the insulin sample. Of these, fasting insulin was better partitioned and could be used for baseline reference interval calculations.

INTRODUCTION

Multiple genes are involved in type 2 diabetes, though the genetic causes are not clear [1-3]. These genes contributed to increased prevalence of type 2 diabetes mellitus in families. Family history of type 2 diabetes in parents resulted in early fasting hyperinsulinemia in non diabetic offspring [4]. The genetic components also contribute to heritability of insulin secretory deficiency [5,6] and metabolic changes [7], resulting in higher prevalence and aggregation of diabetes in families [8], especially among twins [9]. Non genetic inheritance factors may be epigenetic or non epigenetic mechanisms such as familial behaviour and culture. The reported increased maternal transmission of diabetes may result from effects of gestational diabetes on foetus or from maternally inherited mitochondrial genes [10,11].

Partitioning a sample population with reference to a biochemical marker is required for clinical analysis and diagnosis, and to make inferences of clinical or subclinical disease states. Fasting insulin is one such intermediate marker. Partitioning the fasting and post glucose load OGTT insulin is required for analysis of their relationships with other biochemical and clinical parameters [12-14], for establishment of the baseline status and the baseline reference intervals of insulin. Partitioning is also required to understand the heterogeneity and stratification of the intermediate marker with reference to multiple influences [15-18].

In this study, we analysed the relationship of fasting and post glucose load OGTT insulin, as both are likely to be influenced by family history of type 2 diabetes mellitus. If there is a relationship present, then it is likely that both fasting and post glucose load insulin may be partitioned according to family history of type 2 diabetes mellitus.

MATERIALS AND METHODS

This observational, cross-sectional study was done at Amala Institute of Medical Sciences, Haryana, India, in a healthy cross section of participants aged 18 to 25 years. The duration of this study and sample collection was from May 2011 to October 2015. The total sample (n=90) included males (n=31) and females (n=59), and the difference in the number of males and females did not influence the outcome of the study.

Study was approved by the Institutional Research and Ethics Committees (AIMSIEC/01/2011 dated 9/3/2011). Informed written consent was obtained from each participant. Clinical evaluation of volunteers was done for inclusion of individuals without any disease. The participants should be on regular diet, exercise, rest, sleep; had no drugs for one week and all female participants were in the pre gestational period. Clinical biochemistry laboratory evaluation was done for further exclusion of unhealthy individuals at the subclinical level and for evaluating the characteristics of diabetes related variables. Exclusion criteria for these were: BMI >30 kg/m², family history suggestive of obesity and type 1 diabetes, serum triglyceride >250 mg/dl (2.825 mmol/l), waist circumference ≥100 cm, fasting glucose ≥126 mg/dl (7 mmol/L), 2 hour glucose challenged or postprandial glucose >180 mg/dl (10 mmol/L), BP ≥140/90, serum alanine aminotransferase above 125 U/L, hs-CRP >5 mg/l, serum creatinine >1.3 mg/dl (114.9 μmol/L) in males and >1.2 mg/dl (106.1

µmol/L) in females. These abnormal cut off levels were designed for this study and permitted inclusion of individuals with consequences of increased insulin resistance and family history of type 2 diabetes mellitus but excluded the secondary clinical influences.

Blood sample (10 ml) was drawn without anticoagulants after a 10 to 12 hour overnight fasting, between 7.30 and 8.30 in the morning. It was transferred into plastic tubes, centrifuged immediately at 3500 rpm (Remi, India; Table top, swinging bucket rotor centrifuge) for 5 minutes to sediment cells before clotting. Plasma was transferred to glass tubes and incubated for 15 minutes to initiate clotting and clot was separated by a second centrifugation at 3500 rpm for 5 minutes. If clotting was observed after the first centrifugation in the plastic tube, then plasma was allowed to clot in the same tube for 15 minutes and again centrifuged at 3500 rpm for 5 minutes. This procedure reduced haemolysis. Cell lysis cause insulin degradation. All assays were done immediately after preparation of serum.

Analytical Control and Insulin Measurements

Immunochemistry assays were done by the autoanalysers Vitros ECi (Ortho Clinical Diagnostics, USA) and Access 2 (Beckman Coulter, USA). Clinical chemistry assays were done with the autoanalyser Vitros 5,1F S (Ortho Clinical Diagnostics, USA). Insulin assays were done with Access 2 machine with assay reagents and calibrators from Beckman Coulter. Immunometric assay method with magnetic beads coated with anti-insulin antibody was the principle of the insulin assay [19]. Limit of detection of insulin was taken as the lowest insulin concentration distinguishable from zero (calibrator as 0 pmol/L insulin) with 95% confidence, and was 0.21 pmol/L [19,20]. This level of insulin was sufficiently below the lower limit of range of fasting insulin and below the lowest calibrator above zero, of the linear six point insulin calibrator value (an example from a lot is 5.88 pmol/L). Insulin in µU/ml x 6 converted it to pmol/L [21]. The two level internal quality control reagents and the external quality assurance programs were from Biorad Laboratories, Irvine, CA, USA [22]. Claims of the manufacturers of instruments and reagents were validated by internal quality control samples assayed in duplicates for a minimum of ten days or often more. Cross reactivity of assayed serum insulin with proinsulin and C peptide were insignificant [19]. Even weak haemolysis in sample showed marked decrease in insulin due to degradation [19,21] and was the most important interference in the assay. Reference interval of fasting insulin (manufacturer's) was 11.4 to 138 pmol/L [19].

Diagnostic criteria for diabetes mellitus laid by the WHO for fasting plasma glucose were ≥126 mg/dL (7 mmol/L). The criteria for 2 hour postprandial or post glucose load OGTT (75 g in 300 ml water for adults) value was ≥200 mg/dL (11.1mmol/L) [23]. Diabetes mellitus type 2 was differentiated from type 1, by the former having a minimum history of 6 months of glycaemic control by drugs, diet and exercise before insulin injection.

Participants in the sample population were partitioned into those without and with family history of type 2 diabetes mellitus in parents.

STATISTICAL ANALYSIS

Statistical analysis and calculations were done with SPSS, version 23.0 software or manually. Normality of distribution was estimated by Shapiro-Wilk test. Equality or homogeneity of variances of the groups compared was done by Levene's test. Log_{10} transformations converted most of the positively skewed groups to Gaussian distribution and were of equal variances in the groups compared. When variables had Gaussian distribution (before or after transformation) and when there was equality of variance in the groups compared, parametric methods of analysis were used. Otherwise, non parametric methods were used. Differences of fasting insulin of different groups were compared by 95% confidence interval of mean, two-tailed Student's t-test and Mann-Whitney U test [24-26]. There were four missing data in lipid profile (n=86), the missing data did not

influence outcome of the study. The cut off for p-value as a measure of the level of significance was 0.05.

RESULTS

Characteristics of some common diabetes related quantitative variables in the total sample (n=90) are given in [Table/Fig-1]. Mean values of all quantitative variables were within the healthy reference range. Ranges of all quantitative variables were also within the cut off levels permitted by the inclusion/exclusion criteria.

| Quantitative variables n = 90 (Standard units) (Conventional units)	Mean±SD in Standard units (Conventional units)	Range in Standard units (Conventional units)
Age (years)	21.74±2.05`	18 – 25
BMI (kg/m²)	20.71±2.89	15.47 – 27.11
Waist circumference (cm)	75.26±8.51	57.50 – 94.00
Fasting glucose (mmol/L) (mg/dL)	5.16±0.514 (92.92±9.26)	3.97 - 6.87 (71.50 – 123.70)
2 hour OGTT glucose, (mmol/L) (mg/dL)	5.67±1.25 (102.25±22.56)	2.49 – 9.76 (44.86 – 175.80)
Fasting insulin (pmol/L) (µIU/ml)	34.65±17.03 (5.78±2.84)	8.46 – 97.56 (1.41 - 16.26)
30 minute OGTT insulin (pmol/L) (µIU/ml)	382.40±246.66 (63.73±41.11)	69.48 – 1373.40 (11.58 – 228.90)
60 minute OGTT insulin (pmol/L) (µIU/ml)	341.66±243.80 (56.94±40.63)	67.32 – 1612.08 (11.22 – 268.68)
120 minute OGTT insulin (pmol/L) (µIU/ml)	224.24±159.07 (37.37±26.51)	21.06 – 880.50 (3.51 – 146.75)
Total cholesterol (n = 86) (mmol/L) (mg/dL)	4.58 ±0.727 (176.98±28.05)	2.85 - 6.53 (110.00 – 252.00)
Triglycerides (n = 86) (mmol/L) (mg/dL)	0.880±0.357 (77.88±31.64)	0.42 – 2.51 (37 – 222)
LDL cholesterol (n = 86) (mmol/L) (mg/dL)	2.84±0.663 (109.67±25.60)	1.40 – 4.84 (54 - 187)
HDL cholesterol (n = 86) (mmol/L) (mg/dL)	1.34±0.315 (51.67±12.14)	0.73 – 2.20 (28 – 85)

[Table/Fig-1]: Characteristics of type 2 diabetes mellitus related parameters in the sample. OGTT is oral glucose tolerance test.

Visual examination of X-Y scatter diagram [Table/Fig-2] and calculation of Pearson's correlation coefficient [Table/Fig-3] showed significant correlation (r=0.265; p=0.012) of fasting insulin and 30 minute insulin. Similarly, there were significant correlations of fasting insulin with 60 minute (r=0.335; p=0.001) and 120 minute (r=0.277; p=0.008) OGTT serum insulin.

Insulin in groups without and with family history of type 2 diabetes in parents was compared. Fasting insulin in group with family history of diabetes were positively skewed. Log_{10} transformation converted the distribution of most of the samples to Gaussian and had equality of variance [Table/Fig-4]. Percent coefficient of variation (% CV) was found to be lowest in fasting insulin when compared with that of 30, 60 and 120 minute insulin. The lowest % CV was found in fasting insulin from groups with and without family history of diabetes.

Mean fasting insulin was markedly increased in the group with family history of diabetes (p<0.001) but, there was no difference in 30 minute insulin in the groups with and without family history of diabetes mellitus (p=0.574). There was a good increase of 60 (p= 0.002) and 120 minute (p=0.001) OGTT insulin with family history of type 2 diabetes mellitus. These results indicated that fasting insulin showed a better difference between those with and without family history of diabetes mellitus.

Similar differences were also seen in 95% CI of mean of serum insulin [Table/Fig-5]. The CIs with and without family history of diabetes were far separated with fasting insulin, moderately separated with 60 and 120 minute insulin, but was overlapping in 30 minute insulin. These results indicated that there is better partitioning of fasting insulin than post glucose load OGTT insulin with family history of type 2 diabetes.
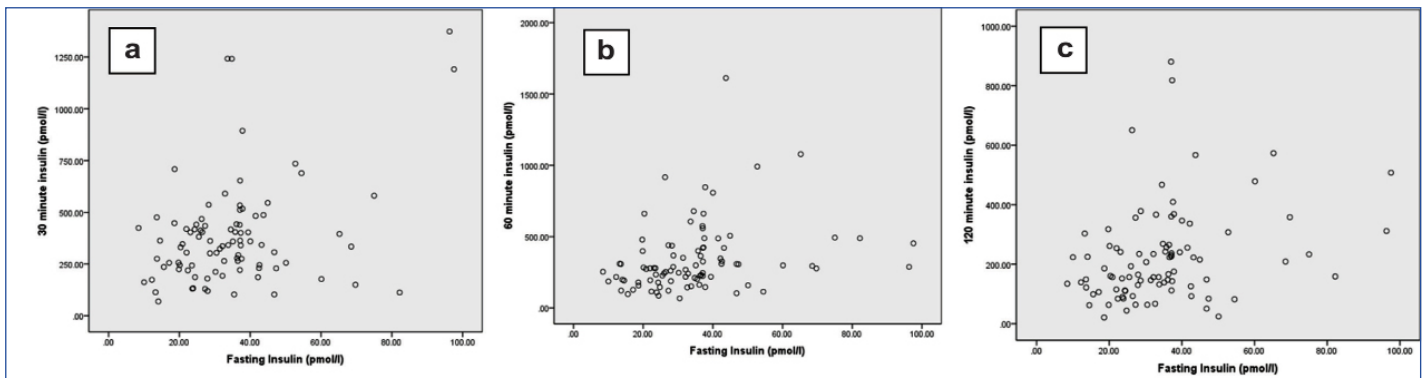
[Table/Fig-2]: X-Y scatter diagram of fasting insulin (0 minute) with 30 (a), 60 (b) or 120 (c) minute oral glucose tolerance test insulin levels.

Row No.	Insulin from OGTT (n = 90)	95% Confidence interval of mean	Shapiro Wilk test P (after $\log_{10}$ transformation)	Correlation coefficient (r)	Significance of correlation p
1.	Fasting pmol/L	31.08 – 38.22	0.236	--	--
2.	30 minute (pmol/L)	330.74 – 434.06	0.262	0.265	0.012
3.	60 minute (pmol/L)	290.60 – 392.73	0.840	0.335	0.001
4.	120 minute (pmol/L)	190.92 – 257.56	0.080	0.277	0.008

[Table/Fig-3]: Pearson's correlation of fasting insulin (Row No. 1) with 30, 60 or 120 minute (Row Nos. 2 – 4) OGTT insulin (after $\log_{10}$ transformation). At least one of the two correlating quantitative variable should have Gaussian distribution by Shapiro Wilk test.

DISCUSSION

Partitioning insulinemia, one of the earliest clinically detectable parameters before onset of type 2 diabetes, was taken up for this study. Fasting glucose and fasting insulin are in a steady state influenced by insulin sensitivity, insulin uptake by tissues and insulin secretion by pancreas [12-14]. All these factors also affected the post glucose challenged OGTT insulin levels. When fasting insulin increased with insulin resistance, post glucose load insulin also increased [12,13]. When insulin resistance increased, insulin secretion also increased to compensate for it [27,28]. This leads to a negative hyperbolic relationship between insulin resistance and insulin secretion [12,13]. These relations between fasting insulin and post glucose challenged insulin are responsible for the correlation between them [Table/Fig-2,3].

Insulin resistance and beta cell insulin secretory dysfunction are the fundamental defects observed in type 2 diabetes. Insulin resistance increased insulin secretion and beta cell dysfunction decreased insulin secretion [12,13]. Both these activities influence fasting insulin in opposing directions and confound each other. It may be reasoned that this confounding of hyerinsulinemia by beta cell secretory dysfunction is the fundamental problem in clinical interpretation of fasting insulin levels.

In addition to the above factors, there is a large increase in glucose-induced insulin secretion during OGTT when compared to fasting insulin. The ability of beta cells to increase secretion of insulin depends on the status of insulin resistance and compensation of insulin resistance by beta cells [12,27,28]. But insulin secretory dysfunction decreased insulin secretion by beta cells. These activities increasing and decreasing insulin secretion act in opposite directions and cause increase %CV of serum insulin. The %CV was found to be lowest in fasting insulin [Table/Fig-4]. Therefore, fasting insulin was found to be more reproducible than glucose challenged insulin of OGTT.

Decrease in hepatic insulin uptake, clearance of plasma insulin and regulation of insulin degradation are considered as causes of hyperinsulinemia [29]. Hyperinsulinemia may be considered as a compensation for insulin resistance which also increases insulin secretion [12,27,28]. Hyperinsulinemia is strongly associated with metabolic syndrome, pathogenesis of type 2 diabetes and obesity [13,14].

Family history of type 2 diabetes was found to have an influence on serum insulin [4]. The influence was more markedly detected in fasting insulin. The decrease in coefficient of variation, standard deviation and standard error of the observed values can increase the significance of the difference between two mean values [Table/Fig-4,5].

Young adults between 18 and 25 years were selected for this study to decrease the influence of growth phase upto 18 years of age and environmental build up after 25 years of age [12-14].

LIMITATION

The 30 minute post glucose load OGTT insulin could not be partitioned, even though it correlated well with fasting insulin which could be partitioned. This early phase of glucose-induced insulin secretion is the most important and the early secretory phase of insulin. At present, we are unable to find a reason for the absence of influence by family history of type 2 diabetes on 30 minute OGTT

Serum insulin (pmol/L)	Without family history of type 2 diabetes (n = 57)		With family history of type 2 diabetes (n = 33)		After $\log_{10}$ transformation			
	Mean ±SD (Range)	Coefficient of variation (%CV)	Mean ±SD (Range)	Coefficient of variation (%CV)	Shapiro-Wilk test for normality p		Levene's test for equality of variances p	Student's t test (or Mann-Whitney U test) p
					Without Family history	With Family history		
Fasting insulin	29.12±10.47 (8.46 - 54.48)	35.95	44.20±21.59 (12.2 - 97.6)	48.84	0.023	0.473	0.491	<0.001
30 minute OGTT insulin	363.98±220.07 (103.2 - 1241.8)	60.46	414.22±287.78 (69.5 - 1373.4)	69.48	0.225	0.940	0.390	0.574
60 minute OGTT insulin	281.34±150.15 (67.3 - 661.2)	53.37	445.86±328.91 (121.3 - 1612.1)	73.77	0.680	0.164	0.544	0.002
120 minute OGTT insulin	189.88±153.96 (21.06 - 880.5)	81.08	283.59±152.17 (63.96 - 650.7)	53.66	0.180	0.536	0.481	<0.001

[Table/Fig-4]: Comparison of insulin concentrations in groups without and with family history of type 2 diabetes mellitus in parents. As groups were positively skewed, $\log_{10}$ transformation was done, followed by Student's t test for Gaussian distributed insulin data or the non parametric Mann Whitney U test.

Serum Insulin (pmol/L)	95% CI of mean	
	Without family history	With family history
Fasting insulin	26.34 – 31.90	36.55 – 51.86
30 minute OGTT insulin	305.59 – 422.37	312.18 – 516.26
60 minute OGTT insulin	241.50 – 321.18	329.23 – 562.49
120 minute OGTT insulin	149.03 – 230.73	229.63 – 337.55

[Table/Fig-5]: Comparison of 95% CI of mean insulin concentrations in groups without and with family history of type 2 diabetes mellitus.

insulin. The secretory phase of insulin has genetic influences and probably only the later phase of OGTT insulin, 60 and 120 minute, are influenced by family history of type 2 diabetes.

CONCLUSION

Fasting insulin correlated well with all post glucose load insulin of OGTT. Fasting, 60 and 120 minute OGTT insulin can be partitioned according to family history of type 2 diabetes mellitus. As the genetic influences are multifactorial, family history of type 2 diabetes would cause stratification and heterogeneity of insulin concentrations in the sample. Of the four insulin parameters, 0 (fasting), 30, 60 and 120 minute OGTT insulin, fasting insulin was better partitioned and could be used for baseline reference interval calculations.

ACKNOWLEDGEMENTS

REFERENCES

[1] Herder C, Roden M. Genetics of type 2 diabetes: pathophysiologic and clinical relevance. Eur J Clin Invest. 2011;41(6):79–92.

[2] Gaulton KJ, Ferreira T, Lee Y, Raimondo A, Mägi R, Reschen ME, et al. Genetic fine mapping and genomic annotation defines causal mechanisms at type 2 diabetes susceptibility loci. Nat Genet. 2015;47(12):1415-25.

[3] Ayub Q, Moutsianas L, Chen Y, Panoutsopoulou K, Colonna V, Pagani L, et al. Revisiting the thrifty gene hypothesis via 65 loci associated with susceptibility to type 2 diabetes. Am J Hum Genet. 2014;94(2):176–85.

[4] Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Increased insulin concentrations in non diabetic offspring of diabetic parents. N Engl J Med. 1988;319(20):1297-301.

[5] Elbein SC, Hasstedt SJ, Wegner K, Kahn SE. Heritability of pancreatic beta – cell function among nondiabetic members of Caucasian familial type 2 diabetic kindreds. J Clin Endocrinol Metab. 1999;84(4):1398-403.

[6] Stumvoll M, Fritsche A, Haring H-U. Clinical characterisation of insulin secretion as the basis for genetic analysis. Diabetes. 2002;51Suppl.1:S122-29.

[7] Tripathy D, Lindholm E, Isomaa B, Saloranta C, Tuomi T, Groop L. Familiality of metabolic abnormalities is dependent on age at onset and phenotype of the type II diabetic proband. Am J Physiol Endocrinol Metab. 2003;285(6):E1297-303.

[8] Valdez R, Liu T, Yoon PW, Khoury MJ. Family history and prevalence of diabetes in the U.S. population. Diabetes Care. 2007;30(10):2517-22.

[9] Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance – a population-based twin study. Diabetologia. 1999;42(2):139-45.

[10] Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000;49(12):2208–11.

[11] Fetita LS, Sobngwi E, Serradas P, Calvo F, Gautier JF. Consequences of fetal exposure to maternal diabetes in offspring. J Clin Endocrinol Metab. 2006;91(10):3718–24.

[12] Khan SE. The relative contribution of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia. 2003;4(1):3-19.

[13] Gerich JE. Contribution of insulin- resistance and insulin- secretory defects to the pathogenesis of type 2 diabetes mellitus. Mayo Clin Proc. 2003;78((4):447-56.

[14] Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999;104(6):787-94.

[15] Clinical and laboratory standards institute (CLSI) document EP28-A3c. Defining, establishing and verifying reference intervals in the clinical laboratory: approved guidelines. 3rd ed. Wayne PA: CLSI, 2008. http://shop.clsi.org/site/Sample_pdf/EP28A3C_sample.pdf

[16] Horowitz GL. Establishment and use of reference values. In: Burtis CA, Ashwood ER, Bruns DE (eds) Tietz textbook of clinical chemistry and molecular diagnostics. 5th Ed. Saunders-Elsevier, New Delhi, 2012:95-118.

[17] Lahti A. Partitioning biochemical reference data into subgroups: comparison of existing methods. Clin Chem Lab Med. 2004;42(7):725–33.

[18] Shirts BH, Wilson AR and Jackson BR. Partitioning reference intervals by use of genetic information. Clin Chem. 2011;57(3):75–81.

[19] Ultrasensitive insulin. In: Procedure manuel. Access II Immunoassay systems, Beckman Coulter, USA. 2005.

[20] Linnet K, Boyd JC. Selection and analytical evaluation of methods – with statistical techniques. In: Burtis CA, Ashwood ER, Bruns DE (eds) Tietz textbook of clinical chemistry and molecular diagnostics. 5th ed. Saunders-Elsevier, New Delhi, 2012:7-47.

[21] Heinemann L. Insulin assay standardization: leading to measures of insulin sensitivity and secretion for practical clinical care. Diabetes Care. 2010;33(6):e83.

[22] Klee GG, Westgard JO. Quality management. In: Burtis CA, Ashwood ER, Bruns DE (eds) Tietz textbook of clinical chemistry and molecular diagnostics. 5th ed. Saunders-Elsevier, New Delhi 2012:163-203.

[23] Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(5):39-53.

[24] Riffenburgh RH. In: Statistics in medicine. 3rd ed. Academic Press, Elsevier, California, USA, 2012:249-353.

[25] Altman DG. Principles of statistical analysis. Comparing groups. In: Practical statistics for medical research. Ist Ed. Chapman & Hall/CRC Press; Florida, USA, 1991:152-271.

[26] Armitage P, Berry G, Matthews JNS. Comparison of several groups. In: Statistical methods in medical research. 4th edition. Blackwell Science Limited, Oxford, UK. 2002:208-35.

[27] Prentki M, Nolan CJ. Islet β cell failure in type 2 diabetes. J Clin Invest. 2006; 116(7):1802–12.

[28] Kasuga M. Insulin resistance and pancreatic beta cell failure. J Clin Invest. 2006; 116(7):1756-60.

[29] Pivovarova O, Bernigau W, Robbert T, Isken F, Möhlig M, Spranger J, et al. Hepatic insulin clearance is closely related to metabolic syndrome components. Diabetes Care 2013;36(11):3779–85.

PARTICULARS OF CONTRIBUTORS:
1. Senior Research Fellow, Department of Biochemistry, Amala Cancer Research Centre, Thrissur, Kerala, India.
2. Professor, Department of Biochemistry, Amala Cancer Research Centre, Thrissur, Kerala, India.
3. Senior Research Fellow, Department of Biochemistry, Amala Cancer Research Centre, Thrissur, Kerala, India.
4. Professor and HOD, Department of Biochemistry, Amala Institute of Medical Sciences, Amala Cancer Research Centre, Thrissur, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Jose Jacob,
Professor and HOD, Department of Biochemistry, Amala Institute of Medical Sciences,
Amala Cancer Research Centre, Thrissur-680555, Kerala, India.
E-mail: jacobj.amala@gmail.com