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Comparative Study of insulin resistance in young adults with and without family history of diabetes

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Abstract:
Background: *India has a large pool of pre-diabeticsubjectsandshowsarapidconversionofthese highrisksubjectstodiabetes.Duetochanginglifestyle Indians arepronetodeveloptype2diabetes(DM)atanearlyage.Insulinresistance(IR)has becomeacentralfeatureinthedevelopmentof impaired glucosetolerance(IGT), type-2diabetes.*
Methods: *100 normal volunteers, 50subjects with and 50 subjectswithoutfamilyhistoryof Diabetes,intheagerangeof18to25yearswereevaluatedforinsulinresistance. Astandard(75g)OGTTwasperformedandplasmaglucoseassessed at0(fasting),30,120min.FastingplasmainsulinlevelsassessedbyRIAkitmethod. UsingFastingPlasmaGlucose(FPG)andFastingPlasmaInsulin(FPI)levelsthe insulin resistanceis calculated by HOMA method.*
Homeostaticmodel assessmentmethodHOMA _IR =FPG(mmol/L) xFPI(μIU / mL) /22.5.
Results:*The Fasting plasmainsulin10.24v/s6.19] (p=0.002) and Insulin ResistancebyHOMA method2.05v/s1.24(p=0.002)ishigherandsignificantinsubjectswithF/Hof DM,BMItobesignificant(p=0.04)insubjectswithF/HofDM.*
Conclusion: *SubjectswithF/HofDMhaddetectableIRatyoungerage .RecognitionofIRinthe pre-diseasestatewouldbebeneficial,asitaffordspotentialimplementationof interventions designedto reducesuch disease development.*
Keywords: *Insulin Resistance; Metabolicsyndrome; Fasting Plasma Insulin (FPI); FastingPlasmaGlucose (FPG);HOMA_IR; Diabetes;*

I. Introduction

IndiahasalargepoolofPre-diabeticsubjects[Impairedglucosetolerance (IGT)andImpairedFastingglucose(IFG)]andshowsarapidconversionofthese highrisksubjectstodiabetes[1].TheIndiancouncilofmedicalresearch(ICMR) studyestimatedthatthecountryalreadyhasaround65.1milliondiabetespatientsand77.2millionpeoplearePre-diabetes[2].Theprevalenceofbothdiabetesand Pre-diabetesincreasesbyage;with60%ofIndianshavingdiabetesorPre-diabetes byage60[3].InIndiansthereisa geneticpredispositiontoIRandtype2diabetesbecauseofgeneticpredisposition obesityinducedIRisgreaterinindividualswithdiabeticfamilyhistorythando individuals from non-diabetic families[5]. Indians h a v e arelativelygreateradiposityatalowerBMIwhencompared withotherethnicgroups,bothwithinandoutsideAsia.[6, 7, 8]ThemajorcomponentofIRappearstobegeneticallydeterminedinmany studies[4, 9]withhighprevalence ofdiabetesrevealedthatlowinsulinsensitivityprecedesandpredictstype2diabetes[4, 9, 10].Insulinresistance(IR)isapathologicalsituationcharacterizedbyalackofphysiologicalresponseofperipheraltissuest oinsulinaction,leadingtothemetabolicandhemodynamicdisturbancesknownasthemetabolic syndrome[11]. Incertainindividuals,InsulinResistance(IR)canprecedetypeIIdiabetesformanyyears,evendecades[12, 13].Hence,recognitionofIRinthepre-diseasestatewouldbebeneficial,asitaffords,potentialimplementationofinterventionsdesigned toreduce suchdiseasedevelopment[9, 10, 14].

Inthisstudy,Homeostaticmodelassessment(HOMA)modelisusedtoquantifyinsulinresistanceandbetacellfunctionfr omfastingplasmaglucose&fastingplasmainsulinlevelsinnon-diabeticyoungadultstodetectearly

occurrenceofInsulinResistanceandtoevaluatethepossibleassociation of familyhistoryof diabetes mellitus.

II. Aims and objectives

1.To detect occurrenceof insulin resistancein healthy youngadults (18-25yrs.)with and without familyhistoryof diabetes mellitus.
2.To studythe impact offamilyhistoryof diabetes in healthy young adults onBMI, lipid profile and insulinresistance

III. Materials &Methods

Studypopulation:

Inthisstudy100normalyoungadultvolunteers,50subjectswithand50subjectswithoutfamilyhistoryofdiabetes,intheagerangeof18to25yearswereevaluatedfor Insulin resistance.

Assays:

Fasting(basal),30,120minvenousplasmaglucoseduringOGTTwasdeterminedbyglucoseoxidasemethodonsiteusingglucoseautoanalyzer.Concentrationsoftotalcholesterol,triglyceride&HDLcholesterolweredeterminedbyenzymatickinetic method using an autoanalyzer.Fastingserumsampleiscollectedfordeterminationofinsulinconcentration.Theserumplasmawasstoredat-20degreeCuntilassayed.CorrespondingSpecificinsulinconcentrationwasdeterminedbyradioimmunoassay(RIA)usingahumanspecificantibodyRIAkit,whichdoesnotcross-reactwithhumanpro-insulin.

StatisticalAnalysis:

Thestudent_t'testhavebeencarriedouttofindthesignificantdifferencebetweenvariousOGTTparameters&indicesbetweensubjectswith&withoutF/HofDM.Chi-quaretesthavebeenusedtofindthesignificantdifferenceoffrequenciesbetweenwith&withoutF/HofDM.ThePearsoncorrelationcoefficientbetweenHOMA_IR and clinical and lab parameters have been computed.

Statisticalsoftware:

TheStatisticalsoftwarenamelySPSS19.0versionusedfortheanalysisofthedata and Microsoft wordandExcel havebeen used to generategraphs, tables etc**.**

IV. Results

Aprospectivestudyconsistingof100normalsubjectswasconducted.Ofthe100subjects,the50subjectswithfamilyhistory&50subjectswithoutfamilyhistoryofDMwasincludedinthestudydepictingbothgroupswherebalancedforfurthercorrelation

Table1:Ageandsexwisedistributionofallsubjectsinthestudy.

Age	Sex		Total
	Male	Female	
18-19	16	29	45
19-20	16	14	30
20-21	11	5	16
21-22	2	1	3
22-23	1	0	1
23-24	0	1	1
24-25	3	1	4
Total	49	51	100

Inthisstudythesexdistributionwasmale:49(49%)andfemale:51(51%)(Table-1Graph-1).Themeanageofthestudypopulationwas19.08(18.0to25.0)years,withStandard Deviation 1.56.(Table: 1)

Table2:DistributionofstudysubjectswithrespecttoF/HofDM.

STUDYSUBJECTS	No	%
StudysubjectswithfamilyHistory		
Parents arediabetic(1st degree)	7	7%
Grandparents are diabetic(2nd degree)	23	23%
Both parents andgrandparents are diabetic	20	20%
Subjectswithoutfamilyhistoryofdiabetes	**50**	**50%**
Total	**100**	**100%**

Of the 50subjectswhohadpositiveF/HofDM,1st degreerelativeswithdiabetes(Parents)was7and2nd degreerelatives(GrandParents)was23andthesubjectswithboth parents andgrandparents arediabeticwas 20.(Table:2)

Table3:Comparisonofclinicalparametersinsubjectswith&withoutF/HofDM.

Clinicalparameters	**WithFamilyhistory**		**Withoutfamilyhistory**		**Statisticalanalysis**		
	Mean	SD	Mean	SD	t	P	Inference
Height	19.00	1.44	19.16	1.68	-0.51	0.61	NS
Weight	78.18	112.26	58.65	10.29	1.22	0.22	NS
BMI	23.24	4.43	21.65	3.39	2.02	0.04	Significant
Waist	75.61	11.74	74.66	8.59	0.46	0.64	NS
Hip	93.86	9.53	91.63	7.56	1.29	0.19	NS
Waist Hip Ratio	5.55	19.00	0.81	0.06	1.76	0.08	NS
Systolic BP	119.92	5.88	121.16	10.58	-0.72	0.47	NS
Diastolic BP	74.08	4.99	73.88	5.33	0.19	0.84	NS

OncomparisonofclinicalparametersinsubjectswithandwithoutF/HofDM,statisticalanalysisfoundBMItobesignifica nt(p=0.04)insubjectswithF/HofDM(Table: 3)

Table4:ComparisonofFPG,FPI,HOMA_IR,HOMA_B%insubjectswith&withoutF/HofDM.

Lab parameters	**WithFamilyhistory**		**Withoutfamilyhistory**		**Statisticalanalysis**		
	Mean	**SD**	**Mean**	**SD**	**t**	**P**	**Inference**
FPG (mmol)	4.58	0.47	4.40	0.59	1.70	0.09	NS
FPI(mU/l)	10.24	8.29	6.19	3.93	3.12	0.002	Significant
HOMA_IR	2.05	1.57	1.24	0.89	3.16	0.002	Significant
HOMA _Beta%	227.63	272.60	179.67	162.76	1.06	0.28	NS

OncomparingsubjectswithandwithoutF/HofDM,statisticalanalysisfoundhighervaluesofFPI10.24v/s6.19(p-0.002)&theHOMA_IR2.05±1.57v/s1.24±0.089(p-value= 0.002) in subjects withF/H ofDM(Table:4)

SincetheprevalentvaluesofIRderivedfromHOMAarenotknownforourpopulation,thecut-offvaluesusedaremeanvaluesfromliterature ofnormoglycemic,impairedglucose tolerantanddiabeticsubjectsofotherpopulations.HOMA_IR value=1isnormal,HOMA_IRvalue=2isseenin5thand 6th decadesubjectswithnormalOGTT,HOMA_IRvalue=3isseeninelderlysubjectswithImpairedGlucoseTolerance[10].

Table5:AssociationofIRbyHOMAmethodinsubjectswithandwithoutF/HofDM

HOMA_IR	WithfamilyH/O	WithoutFamilyH/O	Total
>1	35	27	62
>2	21	9	30
>3	9	2	11
Total	65	38	103

X^2= 5.13, p =0.048 (<0.05) Significant.

AssociationHOMA_IRinsubjectswithF/HofDMisfoundtobestatisticallysignificant (p-value= 0.048). (Table: 5)

Table6:CorrelationofHOMA_IR&clinicalparametersinsubjectswith&withoutfamilyhistoryofdiabetes.

CorrelationofHOMA_IR	WithFamilyhistory			Withoutfamilyhistory		
Clinicalparameters	Pearson"scorrelation	Pvalue	Inference	Pearson"sCorrelation	Pvalue	Inference
BMI	+0.397	0.004	Significant	+0.196	0.17	NS
Waist circumference	+0.31	0.027	Significant	+0.085	0.55	NS
W/H ratio	-0.07	0.62	NS	+0.082	0.57	NS

CorrelationofHOMA_IR&clinicalparameterswith&withoutF/HofDMinstudysubjectsshowedBMI&WCtobesignificantlycorrelatedtoHOMA_IRinsubjectswith F/H ofDM. (Table:6)

Table7:ComparisonofHOMA_IRvaluesinsubjectswith&withoutF/HfDM.

STUDYSUBJECTS	HOMA_IR mean	HOMA_IR SD
StudysubjectswithfamilyHistory	2.05	1.57
□ Parents arediabetic (1st degree)	1.75	1.67
□ Grandparents are diabetic(2nd degree)	1.67	0.93
□ Both parents andgrandparents are diabetic	2.55	2.00
Subjectswithoutfamilyhistoryofdiabetes	1.24	0.89

Of the 100studysubjects,50subjectswithoutF/HofDMtheHOMA_IRwas 1.24±0.89ascomparedtosubjectswithF/HofDM2.05±1.57whereasthe1st degreewas1.75±1.67 &2nd degreewas1.67±0.93&bothwas2.55±2.00.(Table:7) .

Table8:ImpactoffamilyhistoryonHOMA_IRlevelsinstudysubjects.

Relatives	Groups	Number	Mean	SD	„t"test	p-value	Inference
First degree	With F/H	7	1.75	1.67	-2.764	0.008 (<0.005)	Significant
	Without F/H	50	1.24	0.89			
Second degree	With F/H	23	1.67	0.93		0.000	Highly

	Without F/H	50	1.24	0.89	-4.654	<0.001	Significant
Both 1st and 2nd degree	With F/H	20	2.55	2.00	-4.666	0.000 <0.001	Highly Significant
	Without F/H	50	1.24	0.89			

TheHOMA_IRparametershowedstatisticallysignificantimpactduetopositive F/H ofDMonthestudysubjectsin1st degree,2nd degree&both(with1st&2nd degree) groupincomparison with subjects without F/H ofDM.(Table: 8)

V. Discussion

BasedonlongitudinalstudiesinthePimaIndiansatwo-stepmodelfordevelopmentofthediseasewasproposed.Thefirststepistransitionfromnormaltoimpairedglucosetolerance,forwhichinsulinresistanceisthemaindeterminant,andthesecondandlaterstepisworseningfromimpairedglucosetolerancetodiabetes,inwhichbetacelldysfunctionplaysacriticalrole.Thishypothesisisconsistentwithfindings from other ethnicgroups from manyparts of the world[15]

ChanceofDevelopingDiabetes[16]:
Ifsomeonein the familyhas diabetes 20%
Ifone parent has diabetes40%
Ifone parent has diabetesand the other parent is from a diabetic family70%
Ifboth parents have diabetes 99%

Duringthepastfewyearsithasbecomeincreasinglyapparentthatinsulinresistancemaybe a frequent cause of carbohydrate intolerance ora contributing factorhasbeenappreciated.Thesemay bemanifestedbyanincreaseintheconcentrationofinsulinnecessaryforahalfmaximaleffect(decreasedsensitivity)oradecreaseinthemaximal response to insulin (decreased responsiveness), orboth[14].
AcostaAMetalstudiedIRin120subjectswithanormalBMI.MeanHOMA IRwas1.96+/-0.57(range 0.5and3.0).TheyconcludedthattheHOMAvaluesfromtheir studycan beused as reference forChilean non-obese individuals.
Inourstudywehaveestablishedtheinsulinresistancebyhomamethodforoursub-populationwithnormalOGTTintheagerangeof18-25years,HOMA_IR=1.64(0.30-6.91)SD-1.33,HOMA_%BETA=203.65(21.00-1809.52)SD-224.66.Inourstudyof100subjectswithnormalOGTTweobservedafastinginsulin

of8.22µIU(1.6to40.0)andfastingglucoseof81.14mg/dl(64-108).SubjectswithF/HofDMhadhigherbasalinsulinvalueof10.24v/s6.19forsubjectswithoutF/Hof DM (p=0.002) and baseline glucose of 82.44v/s79.2 respectively.(table 4)Inourstudy weobservedsimilarlyincreased fasting plasmainsulininsubjectswithF/H10.24±8.29v/s6.19±3.93IU/ltothosewithoutF/HofDM,FPIwassignificantlyincreasedingroupofsubjectswithF/HofDM(p=0.002).(table 4)
Fastingglucosevalueswereabovethenormalrangein3%ofoursubjects.Thisisinagreementwithanearlierobservationmadeby Raghupathy,etal.inurbansouthIndianyoungadultswheretheyhaveshowna3.8%prevalenceofimpairedfasting glycaemia[17].

BothIndianandwesternpopulationstudieshaveshownthatpredictingindividualsinsulinsensitivityandß-cellfunctionfromBMIispossible ItwasfoundthatBMIwasthemostimportantdeterminantofIR,whileTGandHDL-Clevelsmightbegoodmarkersof IRinnon-obesepatients.Itwasalsoseenthatapositivefamilyhistoryofdiabetesandobesitywereindependentriskfactorsfordevelopment of type2 diabetes[16,18].

ShalitinSetalEstimatedIRin234obesechildrenandadolescents,intheagerangeof5to22yr.IRwasdetectedin81.2%ofthepatients.IRwashighlyprevalentinobesechildrenandadolescents.HenceevaluationforIRusingOGTTisindicatedforallsubjectswithhighrisk[19] .Ourresultsshowedsubjectswith BMI>25had higherIR.InMexicoCityStudy,ß-cellfunctionandIRwereassessedcross-sectionallyusing HOMAin1,449 MexicanswithnormalorIGT.Subjectswere followedupfor3.5yearsinordertoascertaintheincidenceofdiabetesandtoexamineanypossiblerelationshipwithbaselin

eß-cellfunctionandIR.By3.5years,4.4%ofsubjectswithNGTand23.4%withIGThadprogressedtodiabetes.Thedevelopmentofdiabeteswas associated with higher HOMA-IR at baseline.

IntheMalmoPreventiveTrialaprospectivedietandexerciseprogramreducedconversionfromabnormalglucosetolerancetofrankdiabetesby onethird[20].TheFinnishdiabetespreventionstudy andUSDiabetesPreventionProgramshowedarelativeriskreductionof58%withlifestyle interventionsascomparedwithusualcareor placebo[21].Recentclinicaltrials,andanumberoflargecohortstudies,providestrongevidenceonthevalueofphysicalactivityandlifestyleinterventionsforthepreventionoftype2diabetes,hypertensionetc.Bothdietandexercisecanbeeffectivediabetes prevention modalities[20, 21].

VI. Conclusion

InourstudyweobservedthatabnormalIRexistedatamuchyoungerage(18– 25yrs) in subjects with both 1stand 2nd degreeF/H ofDM.ObesityinducedIRisgreaterinsubjectswithF/Hoftype2diabetesthansubjects of non-diabeticF/H.Inthisstudyweobservedthat,subjectswithfamilyhistoryofdiabetes,had higher BMIvalues than subjects without F/Hof DM.Inthepresentstudyweobservedthat,HOMA_IRvaluesaredirectlyproportional to BMIin subjects with F/H ofDM.

InthisstudywealsoobservedwaistcircumferenceisdirectlyproportionaltoHOMA_IR in subjects with F/H of DM.Becauseofstronginfluenceofhereditaryfactorsandhighprevalenceof diabetesinIndians,inthisstudyweobservedearlyoccurrenceofinsulin resistanceinyoungnormoglycemic subjects withF/H ofDM.

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