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The Epidemiology, Aetiology, Pathophysiology, Complications and Pharmacological Study of Types of Diabetes and Their Treatment in Humanbeings

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ABSTRACT
Diabetes Mellitus is an ancient medical term which early physicians used to designate a mysterious disease characterized by profuse, sweet-tasting urine. As medicine progressed the meaning of the term changed considerably. Unfortunately, the concept that diabetes mellitus is a disease-a distinct pathological entity has persisted and has caused much confusion both among the general public and within the health care professions. In fact, diabetes is a highly complex phenomenon which defies any simple explanation. It increases the risk of multiple complications including retinography, nephropathy, and atherosclerotic disease. Management strategies include management of the associated metabolic risk factors such has hyperglycemia, dyslipidemia, and hypertension. Most experiments are carried out on rodents, even though other species with human-like biological characteristics are also used. Animal models develop diabetes either spontaneously or by using chemical, surgical, genetic or other techniques, and depict many clinical features or related phenotypes of the disease.

Keywords: Diabetes Mellitus, complications,nephropathy, retinography, Animal models

INTRODUCTION

Itisametabolicdisordercharacterizedbyhyper-glycaemia,glycosuria,negativenitrogenbalanceandsometimesketonemia.Awide-spreadpathologicalchangeisthickeningofcapillarybasementmembrane,increaseinvesselwallmatrixandcellularproliferationresultinginvascularcomplicationslikelumennarrowing,earlyatherosclerosis,andsclerosisofglomerularcapillaries,retinopathy,neuropathyandperipheralvascularinsufficiency[1].

DiabetesMellitusisaconstitutionaldisease.Itisalsoknownas“DiseaseofCivilization”(Urbanization)seenmoreincitiesthanvillages.Buthoweveritisnowmakingi nroadsintoIndianvillages.Diabetesisanimportanthumanailmentafflictingmanyfromvariouswalksoflifeindifferentcountries[2-5].Itisanoutcomeofsedentarylifestyle&incorrectfood habits.No.ofpeopleafflictedbyDiabetesMellitusisincreasingeachday.9-12%populationofworldhaseitherestablishedDiabetesMellitus(or)tendencyofcontractingitinnearfuture.18MillionsofIndiansaresufferingfromDiabetesMellitus.Thoughitisrampanttoday,itisnotanewdisease.Itis well-knownfromhistorictimes.Wellknownayurvedicphysicians MaharshiCharaka(600BC)&Sushrutha(400BC)correctlydescribedalmostallthesymptomsofthisdiseaseandcalleditas“MadhuMeha”(ashowerofhoney) andexplainedinayurvedicliteraturecalled‘Sushrutha Samhitha’.Afterthediscoveryofinsulin,peoplehadstartedbelievingthatDiabetesMellituswillsoonbebanished fromtheearth.Howeverthisbeliefhasturnedouttobeadream&provedfallacious.Withvigoroustreatment,short-termcomplicationsofDiabetesMellituscanbechecked;butitslong-termcomplicationscanbehardlybeingprevented[6,7].

Historyofdiabetesmellitus:

Diabetesisoneoftheoldestknowndiseases.AnEgyptianmanuscriptfromc.1550BCEmentionsthephrase“the passingoftoomuchurine.”ThegreatIndianphysicianSushrutaidentifiedthediseaseandclassifieditasMedhumeha.TheancientIndianstestedfordiabetesbyobservi

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ngwhetherantswereattractedtoaperson'surine,andcalledtheailment"sweeturinedisease"(Madhumeha).Concerningthesweetnessofurine,itistobenotedthattheChinese,JapaneseandKoreanwordsfordiabetesarebasedonthesameideographswhichmean"sugarurinedisease".Itwasin1776thatMatthewDobsonconfirmedthatthesweettastecomesfromanexcessofakindofsugarintheurineandblood[8-11].

Thefirstcompleteclinicaldescriptionofdiabeteswasgivenbythe AncientGreekphysicianAretaeusofCappadocia(fl.1stcenturyCE),whonotedtheexcessiveamountofurinewhichpassedthroughthekidneysandgavethediseasethename“diabetes”.Diabetesmellitusappearstohavebeenadeathsentenceintheancientera.Hippocratesmakesnomentionofit,whichmayindicatethathefelttthediseasewasincurable.InmedievalPersia,Avicenna(980–1037)providedadetailedaccountondiabetesmellitusinTheCanonofMedicine,"describingtheabnormalappetiteandthecollapseofsexualfunctions,"andhedocumentedthesweettasteofdiabeticurine[12-15].

Avicennarecognizedprimaryandsecondarydiabetes. Healsodescribeddiabeticgangrene,andtreateddiabetesusingamixtureoflupine,trigonella(fenugreek),andzedoaryseed,whichproducesaconsiderablereductionintheexcretionofsugar,atreatmentwhichisstillprescribedinmoderntimes.Avicennaalso"describeddiabetesinsipidusverypreciselyforthefirsttime",thoughitwaslaterJohannPeterFrank(1745–1821)whofirstdifferentiatedbetweendiabetesmellitusanddiabetesinsipidus.Althoughdiabeteshasbeenrecognizedsinceantiquity,andtreatmentsofvarioused efficacieshavebeenknowninvariousregionssincetheMiddleAges,andinlegendformuchlonger,pathogenesisofdiabeteshasonlybeenunderstoodexperimentallysinceabout1900[16].

In1910,SirEdwardAlbertSharpey-Schafersuggestedthatpeoplewithdiabeteswerede ficientinasinglechemicalthatwasnormallyproducedbythepancreas;heproposedcallingthissubstanceinsulin,fromtheLatininsula,meaningisland,inreferencetotheinsulin-producingisletsofLangerhansinthepancreas[17].Insulinproductionandtherapyrapidlyspreadaroundtheworld,largelyasaresultofthisdecision.Bantingishonoredby WorldDiabetesDaywhichisheldonhisbirthday,November14.Thedistinctionbetweenwhatisnowknownastype1diabetesandtype2diabeteswasfirstclearlymadebySirHaroldPercival(Harry)Himsworth,andpublishedinJanuary1936.Despitetheavailabilityoftreatment, diabeteshasremainedamajorcauseofdeath.Forinstance,statisticsrevealthatthecause-specificmortalityrateduring1927amountedtoabout47.7per100,000populationsinMalta[18].

Otherlandmarkdiscoveriesinclude[19-21]:

- Identificationofthefirstofthesulfonylureasin1942
- Reintroductionoftheuseofbiguanidesfor Type2diabetesinthelate1950s.Theinitialphenforminwaswithdrawnworldwide(intheU.S.in1977)duetoitspotentialforsometimesfatallacticacidosisandmetforminwasfirstmarketedinFrancein1979,butnotuntil1994intheUS.
- Thedeterminationoftheaminoacidsequenceofinsulin(bySirFrederickSanger,forwhichherecevedaNobelPrize)
- Theradioimmunoassayforinsulin,asdiscoveredbyRosalynYalowandSolomonBerson(gainingYalowthe1977NobelPrizeinPhysiologyorMedicine)
- Thethree-dimensionalstructureofinsulin(PDB2INS)
- DrGeraldReaven'sidentificationoftheconstellationofsymptomsnowcalledmetabolicsyndromein1988
- Demonstrationthatintensiveglycemiccontrolintype1diabetesreduceschronicsideeffectsmoreasglucoselevelsapproach'normal'inalargelongitudinalstudy,andalsointype2diabeticsinotherlargestudies
- Identificationofthefirstthiazolidinedioneasaneffectiveinsulinsensitizerduringthe1990s

In1980,U.S.biotechcompanyGenentechdevelopedbiosynthetichumaninsulin.Theinsulinwasisolatedfrom geneticallyalteredbacteria(thebacteriacontainthehumangeneforsynthesizingsynthetichumaninsulin),whichproducelargequantitiesofinsulin.Thepurifiedinsulinisdistributedtopharmaciesforusebydiabetespatients.Initially,thisdevelopmentwasnotregardedbythemedicalprofessionasaclinicallymeaningfuldevelopment.In1996,theadventofinsulinanalogueswhichhadvastlyimprovedabsorption,distribution,metabolism,andexcretion(ADME)characteristicswhichwereclinically meaningfulbasedonthisearlybiotechnologydevelopment[22,23].

Epidemiologyofdiabetesmellitus: Theprevalenceof diabetesmellitusisincreasingwithageingofthepopulationandlifestylechangesassociatedwithrapidurbanizationandwesternization.Thediseaseisfoundinallpartsoftheworldandisrapidlyincreasinginitscoverage[24].

Prevalenceandincidenceofdiabetesmellitus: Globally,theprevalenceofdiabeteswithouttypedistinction wasestimatedtobe4%in1995.AccordingtoWHO,itisestimatedthat3%oftheworld’spopulationhavediabetesandtheprevalenceisexpectedtodoublebytheyear2025to6.3%.Therewillbea42%increasefrom51to72millioninthedevelopedcountriesand170%increasefrom

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84to228million,inthedevelopingcountries[25,26].Thus, bytheyear2025,over75%ofallpeoplewithdiabeteswil lbeinthedevelopingcountries,ascomparedto62%in19 95.

Thereasonsbehindthisprojectedincreaseinprevalenc eratearedueto urbanization,westernizationandtheiras sociatedlifestylechanges,increaseinlifeexpectancyat birth,physicalinactivityandobesityandpossiblyagene ticpredisposition.Age,ethnic,regionalandracialdiffer enceshavealsobeenfoundtoplayaroleforthediabeticin cidenceinheterogeneouspopulationswithinthesamea rea[27].

Aetiologyofdiabetesmellitus:

- Heredity:Itisstronglybelievedthatduetosomege neswhichpassfromonegenerationtoanother,aper soncaninheritdiabetes.Itdependsuponcloseness ofbloodrelationshipasmotherisdiabetic,theriskis 2to3%,fatherisdiabetic,theriskismorethanthepre viouscaseandifboththeparentsarediabetic,thechi ldhasmuchgreaterriskfordiabetes.Thereisagenet icelementinindividualsusceptibilitytosomeofth esetriggerswhichhasbeentracedtoparticularHL Agenotypes(i.e.,thegenetic"self"identifiersrelie duponbytheimmunesystem)[28].However,evenint hosewhohaveinheritedthesusceptibility,type1di abetesmellitusseemstorequireanenvironmentalt rigger.
- Obesity:Beingoverweightmeansincreasedinsuli nresistancethatisifbodyfatismorethan30%,BMI 25+,waistgrith35inchesinwomenor40inchesin males.
- IncorrectDietaryhabits(MalnutritionRelatedDia betes):Impropernutrition,lowproteinandfiberint ake,highintakeofrefinedproductsaretheexpected reasonsfordevelopingdiabetes
- InadequatePhysicalwork:Peoplewithsedentaryl ifestylearemorepronetodiabetes,whencompared tothosewhoexercisethriceaweek,areatlowriskof fallingpreytodiabetes.
- Infections:Someofthestrephylococciissupposed toberesponsiblefactorforinfectioninpancreas.So meoftherusknownascoxsackieB4isresponsibl efortype1diabetes.
- Sex:Diabetesiscommonlyseeninelderlyespecial lymalesbut,stronglyinwomenandthosefemales withmultiplepregnancyorsufferingfrom(PCOS) PolycysticOvarianSyndrome.
- Side-effectsofcertaindrugs:Clozapine(Clozaril),olan zapine(Zyprexa),risperidone(Risperdal),quetia pine(Seroquel)andziprasidone(Geodon)arekno wntoinducethislethaldisease
- OtherIllness:
  - ✓ Hypertension:Ithadbeenreportedinmanystudies thatthereisdirectrelationbetweenhighsystolicpr essureanddiabetes.
  - ✓ Serumlipidsandlipoproteins:Hightriglyceridean dcholesterollevelinthebloodisrelatedtohighbloo dsugars,insomecasesithasbeenstudiedthatriskisi nvolvedevenwithlowHDLlevelsincirculatingbl ood.
  - ✓ Psychologicalfactors:Eitherphysicalinjuryorem otionaldisturbanceisfrequentlyblamedastheiniti alcauseofthedisease.AnydisturbanceinCorticost eroidorACTHtherapymayleadtoclinicalsignsoft hedisease.

Othercausesofdiabetes[29,30]:

- ❖ Abnormalityingluco-receptorofβ-cellssothattheyrespondathigherglucoseconcentr ation.
- ❖ Reducedsensitivityofperipheraltissuestoinsulin: reductioninnumberofinsulinreceptors,'downreg ulation'ofinsulinreceptors.Manyhypertensivesa rehyperinsulinemicbutnormoglycaemic;exhibit insulinresistance.Hyperinsulinemicpersehasbee nimplicatedincausingangiopathy.
- ❖ Excessofhyperglycemichormones(glucagon'set c.)/obesity:causerelativeinsulindeficiency— theβ-cellslagbehind.

Symptomsofdiabetesmellitus:

Mostly30%DiabetesMellituscasesarediagnosedsym ptomaticallybyfollowingsymptoms.inearlierstageso fdisease,whilerests of cases areasymptomaticanddiagnosedaccidently.Diabetes Mellitususuallyaffectsvariousorgans(or)systemsofb odygivesrisetosuchsymptomsasmouldsometimesmi sleadevenaphysician[31].

- ❖ Polyurea(Excessive&frequenturination):S ugarescapesinurinedragsalargequantityofwateralon gwithit.
- ❖ Polydipsia(Drynessofmouth&excessivethi rst):Torestorefluidlossbyexcessiveurination.
- ❖ Polyphagia(Excessivehunger):InDiabetes Mellitusglucosecan'tenterthevariousbodycells.Thus cellsstarveinspiteofbeingbathedbyglucosestream.To overcomethiscellularstarvation,thebodygivesrisetoa bnormal&Excessivehunger.
- ❖ Lossofweight:Becauseofstarvationofgluco se.Bodydisintegratesstoredfatsforcellularnourishme nt.
- ❖ Weakness,Fatigue&Bodyache:Bodyalsodisinte gratesstoredMuscle-Proteintonourishstarvingcells.
- ❖ Mentalfatigue&lackofconcentration:Asbraincel lshavetodependchieflyonglucosefortheirnouris hment.Howevertheycannotutilizetheavailablegl

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ucose,duetowhichpersonexperiencesunduementalfatigue,cannotconcentrateandbecomesforgetful.

- Wound-infectionanddelayedhealing:Glucose-richbloodisagoodbreedingmediumforpusforming micro-organismsandalsoeffectssmallBloodvessels,(microangiopathy)nerve(neuropathy)leadingtodecreaseinbloodsupplyofskinandderangementofskinstriation.Thereforewoundonadiabeticpatientsbodygeteasilyinfectedandfailstoheal.
- Easysusceptibilitytoinfectionsofskin,gum&respiratorytract:glucoserichbloodisagoodbreeding mediumformicroorganismsandhormonalimbalancecausesdecreaseinimmunitypowerandeasilycontractsinfectionsofskin,gumandrespiratorytractinfections.Itmayalsocausesboils,carbuncles,cough,coldandpyorrhea.
- Intenseitchingalloverthebody:irritationofnerveendingsofskinandgenitalorgansduetoexcessiveglucoseintheblood.
- Frequentchangesinthesharpnessofvisionandspectaclenumbers:changesintheglucoseconcentrationofinternalaqueousfluidofeyesleadstovariationinthefocusingpower.Hencepatienthastochange spectaclelensnumber.Thecrystallinelensofeyedependsfortheirnourishmentandtransparencyontheglucosedissolvedintheaqueous.Inthediabetes mellitusthenourishmentofcrystallinelensisjeopardized,leadstoanuntimelycataract.
- Achingornumbnessoflimbsandanabnormalincreaseordecreaseinskin-sensations:diabetesuntowardlyaffects thosenervoussystemstogiverisetothesesymptoms.
- Sexualdebilityorimpotence:Generalweakness,disintegrationofmuscleprotein,mentaldepression undesirablechangesinbloodcirculatoryandnervoussystemgiverisetothesesymptoms.
- Diabeticunconsciousness(hyperglycemiccoma) :fatdisintegrationleadstoproductionofketonebodiesinbloodandincreaseintheirlevelscauses'bloodacidicandgraduallyleadstounconsciousness. Howevermaturityonsetdiabetescreepsintobodysosilentlythatthevictimusuallyremainsunawareandsymptomless[32].

Typesofdiabetesmellitus

WHOclassificationofdiabetesintroducedin1980andrevisedin1985wasbasedonclinicalcharacteristics.Thetwomostcommontypesofdiabeteswereinsulin-dependentdiabetesmellitus(IDDM)or(typeI)andnon-insulin-dependentdiabetesmellitus(NIDDM)or(typeII).WHOclassificationalsorecognizedmalnutrition-relateddiabetesmellitusandgestationaldiabetes.Malnutrition-relateddiabeteswasomittedfromthenewclassificationbecauseitsetiologyisuncertain,anditisunclearwhetheritisaseparatetypeofdiabetes[33].

TypeIdiabetesmellitus: Itisaresultofcellularmediatedautoimmunedestructionoftheinsulinsecretingβ-cellsofthepancreas,whichresultsinanabsolutedeficiencyofinsulinforthebody.Patientsaremorepronetoketoacidosis.Itoccursinchildrenandyoung,usuallybefore40yearsofage,althoughdiseaseonsetcanoccuratanyage.ThepatientwithtypeIdiabetesmustrelyoninsulinmedicationforsurvival.Itmayaccountfor5-10%ofalldiagnosedcasesofdiabetes.Autoimmune,geneticandenvironmentalfactorsarethemajorriskfactorsfortypeIdiabetes.
Diabeticketoacidosisiscausedbyreducedinsulinlevels,decreasedglucoseuse,andincreasedgluconeogenesisfromelevatedcounterregulatoryhormones,including catecholamines,glucagon,andcortisol.Primarilyitaffectspatientswithtype Idiabetes,butalsomayoccurinpatientswithtype2diabetes.Patientswithdiabeticketoacidosisusuallypresentwithpolyuria,polydypsia,polyphagia,andweakness[34].

TypeIIdiabetesmellitus: Twokeyfeaturesinthepathogenesisoftype IIdiabetesmellitusareadecreasedabilityofinsulintostimulateglucoseuptakeinperipheraltissues,insulinresistance,andtheinabilityofthepancreaticβ-celltosecreteinsulinadequately,β-cellfailure.Themajorsitesofinsulinresistanceintype2diabetesaretheliver,skeletalmuscleandadiposetissue. Bothdefects,insulinresistanceandβ-cellfailure,arecausedbyacombinationofgeneticandenvironmentalfactors.Environmentalfactorssuchaslifestylehabits(i.e.,physicalinactivityandpoordietaryintake),obesityandtoxinsmayactasinitiatingfactorsorprogressionfactorsfortypeIIdiabetes.Thegeneticfactorsarestillpoorlyunderstood.
TypeIIdiabetesisincreasinglybeingdiagnosedatanyagenowadaysanditaccountsfor90-95%ofalldiagnosedcasesofdiabetes.Itisassociatedwitholdage,obesityfamilyhistoryofdiabetes,impairedglucosemetabolism,physicalinactivity,andrace /ethnicity[35].

Gestationaldiabetesmellitus: Gestationaldiabetes,bloodglucoseelevationduringpregnancy,isasignificantdisorderofcarbohydratemetabolismduetohormonal changeduringpregnancy,whichcanleadtoelevatedblodglucoseingeneticallypredisposedindividuals.Itismorecommonamongobesewomenandwomenwithafa

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milyhistoryofdiabetes.Itusuallyresolvesoncethebabyisborn,however,afterpregnancy,5-10%ofwomenwithgestationaldiabetesarefoundtohavetypeIIdiabetesand20-50%ofwomenhaveachanceofdevelopingdiabetesinthenext5-10years[36].
Otherformsofdiabetesmellitusinclude:

Congenital diabetes:-whichisduetogeneticdefectsofinsulinsecretion.
Cystic fibrosis:-relateddiabetes,steroiddiabetesinducedbyhighdoses of glucocorticoids.
Pre-diabetesisacommonconditionrelatedtodiabetes.Inpeoplewithpre-diabetes,thebloodsugarlevelishigherthannormalbutnothighenoughtobeconsidered diabetic. Pre-diabetesincreasesyourriskofdevelopingtype2diabetesandofheartdiseaseorstroke.Pre-diabetescantypicallybereversedwithoutinsulinormedicationbylosingamodestamountofweightandincreasingyourphysicalactivity.Thisweightlosscanprevent,oratleastdelay,theonsetoftype2diabetes.
AninternationalexpertcommitteeoftheAmericanDiabetesAssociationredefinedthecriteriaforpre-diabetes,loweringthebloodsugarlevelcut-offpointforpre-diabetes.Approximately20%moreadultsarenowbelievedtohavethisconditionandmaydevelopdiabeteswithin10yearsiftheydonotexerciseormaintainahealthy weight.
About17millionAmericans(6.2%ofadultsinNorthAmerica)arebelievedtohavediabetes.Aboutonethirdofdiabeticadultsdonotknowtheyhave diabetes.
About1millionnewcasesoccureachyear,anddiabetesisthedirectorindirectcauseofatleast200,000deathseachyear[37].
Theincidenceofdiabetesisincreasingrapidly.Thisincreaseisduetomanyfactors,butthemostsignificantaretheincreasingincidenceofobesityandtheprevalenceofsedentary lifestyles.
"Diabetesisoneofthemostcostlyofchronicdiseases,accountingfor$174billioninmedicalcareeachyearintheUnitedStates,withthecostofcareforpatientswithdiabetesaveraging2.3timeshigherthansimilarpatientswithoutdiabetes,"saidRobertGabbay,wholedtheinvestigation.Headdedthatthemodelofcarecouldhelpcontrolcosts.

Diagnosis of diabetes mellitus:
Diabetesmellitusischaracterizedbyrecurrentorpersistenthyperglycemia,andisdiagnosedbydemonstratinganyoneofthefollowing:

•Fastingplasmaglucoselevel≥7.0mmol/L(126mg/dL).
•Plasmaglucose≥11.1mmol/L(200mg/dL)twohoursaftera75goralglucoseloadasinaglucosetolerancetest.
•Symptomsofhyperglycemiaandcasualplasmaglucoseglucose≥11.1mmol/L(200mg/dL).
•Glycatedhemoglobin(HbA1C)≥6.5%.
Apositiveresult,intheabsenceofunequivocalhyperglycemia,shouldbeconfirmedbyarepeatofanyoftheabove-listedmethodsonadifferentday.Itispreferabletomeasureafastingglucoselevelbecauseoftheeaseofmeasurementandtheconsiderabletimecommitmentofformalglucosetolerancetesting,whichtakestwohourstocompleteandoffersnoprognosticadvantageoverthefastingtest.Accordingtothecurrentdefinition,twofastingglucosemeasurementsabove126mg/dL(7.0mmol/L)isconsidereddiagnosticfordiabetesmellitus.Peoplewithfastingglucoselevelsfrom100to125mg/dL(5.6to6.9mmol/L)areconsideredtohaveimpairedfastingglucose.Patientswithplasmaglucoseatorabove140mg/dL(7.8mmol/L),butnotover200mg/dL(11.1mmol/L),twohoursaftera75goralglucoseloadareconsideredtohaveimpairedglucosetolerance.Ofthesetwopre-diabeticstates,thelatterinparticularisamajorriskfactorforprogressiontofull-blowndiabetesmellitusaswellascardiovascular disease[38].

Pathophysiology of diabetes mellitus:
Thepancreasplaysaprimaryroleinthemetabolismofglucosebysecretingthehormonesinsulinandglucagon.TheisletsofLangerhanssecreteinsulinandglucagondirectlyintotheblood.Insulinisaproteinthatisessentialforproperregulationofglucoseandformaintenanceofproperbloodglucoselevels.
Glucagonisahormonethatopposestheactionofinsulin.Itissecretedwhenbloodglucoselevelfalls.Itincreasesbloodglucoseconcentrationpartlybybreakingdownstoredglycogenintheliverbyapathwayknownasglycogenolysis.Gluconeogenesisistheproductionofglucoseintheliverfromnon-carbohydrateprecursorssuchasglycogenicaminoacids.
Thoughpathophysiologyofdiabetesremainstobefullyunderstood,experimentalevidencessuggesttheinvolvementoffreeradicalsinthepathogenesisofdiabetesandmoreimportantlyinthedevelopmentofdiabeticcomplications.Freeradicalsarecapableofdamagingcellularmolecules,DNA,proteinsandlipidsleadingtoalteredcellularfunctions.Manyrecentstudiesrevealthatantioxidantscapableofneutralizingfreeradicalsareeffectiveinpreventingexperimentallyinduceddiabetesinanimal

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modelsaswellasreducingtheseverityofdiabeticcomplications[39].
Insulinistheprincipalhormonethatregulatesuptakeofglucosefromthebloodintomostcells(primarilymuscleandfatcells,butnotcentralnervoussystemcells).Thereforedeficiencyofinsulinortheinsensitivityofitsreceptorsplaysacentralroleinallformsofdiabetesmellitus.
Humansarecapableofdigestingsomecarbohydrates,inparticularthosemostcommoninfood;starch,andsomedisaccharidessuchassucrose,areconvertedwithinafewhourstosimplerformsmostnotablythemonosaccharideglucose,theprincipalcarbohydrateenergysourceusedbythebody.Therestarepassedonforprocessingbygutfloralargelyinthecolon.Insulinisreleasedintothebloodbybetacells(β-cells),foundintheIsletsofLangerhansinthepancreas,inresponsetorisinglevelsofbloodglucose,typicallyaftereating.Insulinisusedbyabouttwo-thirdsofthebody'scellstoabsorbglucosefromtheblood foruseasfuel,forconversiontootherneededmolecules, orforstorage.
Insulinisalsotheprincipalcontrolsignalforconversion ofglucosetoglycogenforinternalstorageinliverandmusclecells.Loweredglucoselevelsresultbothinthereducedreleaseofinsulinfromthebetacellsandintherevers econversionofglycogentoglucosewhenglucoselevels fall.Thisismainlycontrolledbythehormoneglucagon whichactsintheoppositemannertoinsulin.Glucosethusforciblyproducedfrominternallivercellstores(asglycogen)re-enterstheblood stream;musclecellslackthenecessaryexportmechanism.Normallylivercellsdothiswhenthelevelofinsulinislow(whichnormallycorrelateswithlowlevelsofbloodglucose).
Higherinsulinlevelsincreasesomeanabolic("building up")processessuchascellgrowthandduplication,proteinsynthesis,andfatstorage.Insulin(oritslack)istheprincipalsignalinconvertingmanyofthebidirectionalprocessesofmetabolismfromacatabolictoananabolicdirection,andviceversa.Inparticular,alowinsulinlevelisthetriggerforenteringorleavingketosis(thefatburningmetabolicphase)[40].
Iftheamountofinsulinavailableisinsufficient,ifcellsrespondpoorlytotheeffectsofinsulin(insulininsensitivityorresistance),oriftheinsulinitselfisdefective,thenglucosewillnothaveitsusualeffectsothatglucosewillnotbeabsorbedproperlybythosebodycellsthatrequireitnorwillitbestoredappropriatelyintheliverandmuscles.
Theneteffectispersistenthighlevelsofbloodglucose,poorproteinsynthesis,andothermetabolicderangements,suchasacidosis.
Whentheglucoseconcentrationinthebloodisraisedbeyonditsrenalthreshold(about10mmol/L,althoughthismaybealteredincertainconditions,suchaspregnancy), reabsorptionofglucoseintheproximalrenaltubuliisincomplete,andpartoftheglucoseremainsintheurine(glycosuria).Thisincreasestheosmoticpressureoftheurine andinhibitsreabsorptionofwaterbythekidney,resultinginincreasedurineproduction(polyuria)andincreased fluidloss.Lostbloodvolumewillbereplacedosmotically fromwaterheldinbodycellsandotherbodycompartments,causingdehydrationandincreasedthirst[41].

Drug therapy for diabetes mellitus:
Theaimoftreatmentistokeepthebloodsugarlevelswithinnormallimitsandpreventcomplicationsofdiabetes.
1.ForIDDM(Insulindependentdiabetesmellitus)insulintherapywasdone.
2.ForNIDDM(Non-insulindependentdiabetesmellitus)oralhypoglycemicareusedforthearpy.
1. FortherapyofIDDM:Insulinisanhoromonederivedfromhuman,beef,porkpancreas. Dose is about 100U/ml and is giventhroughi.v(or)s.c
2.Fortherapyof NIDDM: Oral Hypoglycemics

- Metformin-500mg(onceortwiceaftermeals,increasingat2-4 week intervaltoamaximumof3gms/day)
- Sulphonylureasfornon-obese regimen; gliclazide-80mg/dayorallybeforethemealoftheday.
- Thedoseisadjustedaccordingto response, at2-4weeksintervalsbyincrementsof40-80mg,toamaximumof320mg/day.
- When therapy oforal hypoglycemic failstheninsulin therapy wasdone.

3.Fordiabetic ketoacidosis: Solubleinsulin1units/mlini.vrouteisusedfortherapy. Intravenousfliuds&electrolytesarepreferable[42].

Complications of diabetes mellitus:
Forthedevelopmentofdiabeticcomplications,theabnormalitiesproducedinlipidsandproteinsarethemajoretiologicfactors.Indiabeticpatients,extra-cellularandlonglivedproteins,suchaselastin,laminin, collagenarethemajortargetsoffreeradicals.Theseproteinsaremodifiedtoformglycoproteinsduetohyperglycemia.Themodificationoftheseproteinspresentintissuessuchaslens,vascularwallandbasementmembranes areassociatedwiththedevelopmentofcomplicationsofdiabetessuchascataracts,microangiopathy,atherosclerosisandnephropathy.Duringdiabetes,lipoproteinsareoxidizedbyfreeradicals.Therearealsomultipleabnormalitiesoflipoproteinmetabolisminverylowdensitylipoprotein(VLDL),lowdensitylipoprotein(LDL),anddhighdensitylipoprotein(HDL)indiabetes.Lipidpero

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xidationisenhancedduetoincreasedoxidativestressin diabeticcondition.Apartfromthis,advancedglycation endproducts(AGEs)areformedbynon-enzymaticglycosylationofproteins.AGEstendtoaccumulateonlong-livedmoleculesintissuesandgenerateabnormalitiesincellandtissuefunctions.Inaddition,AGEsalsocontributetoincreasedvascularpermeabilityinbothmicroandmacrovascularstructuresbybindingtospecificmacrophagereceptors.Thisresultsinformationoffreeradicalsandendothelialdysfunction.AGEsarealsoformedonnucleicacidsandhistonesandmaycausemutationsandalteredgeneexpression[43].

AcutecomplicationsofDiabetes: Diabeticcoma(unconsciousness):-
MostcommoninjuvenileDiabetics.Beforediscoveryofinsulinmorethanhalfofjuvenile Diabetesdiedofdiabeticcoma.
Unconsciousnessenvieswhentheconcentrationofglucoseinthebloodrises(hyperglycemia)decreases(hypoglycemia),Disintegrationofstoredfatinsidebodyiscommeasuredwiththeamountofglucoseinblood.EndproductsofFatdisintegrationareketonebodiesmakebloodacidicandourbodytriestogetridoftheseketonebodiesbyproducingmoreurinehenceresultinreductioninFluidcontentofbloodAcidifiedbloodaffectsbraintogivesrisetodrowsinessandlethargyandgraduallydiabeticcoma[24,29].

ChroniccomplicationsofDiabetes: Thechroniccomplicationsofdiabetesmellitusaffectmanyorgansystemsandareresponsibleforthemajorityofmorbidityandmortality(MclnnesAD2012).Itcanbedividedasvascularandnonvascularcomplications(ChanCNetal;2011).Vascularcomplicationsaresub-dividedintomicrovascularretinopathy,neuropathy,nephropathyandmacrovascularcomplicationsarecoronaryarterydisease,peripheralvasculardiseaseandcerebrovasculardisease.Nonvascularcomplicationsincludeproblemssuchasgastroporesis,sexualdysfunctionandskinchanges.

Diabeticneuropathy: MostcommoncomplicationsofNervoussystemarederapgementsoftouchsensationsometimesthetouchsensationbecomesabnormallyacute(hyper-aesthesia)patientexperiencesduringsensationinhislimbsandmoretroubledduringnight.Atothertimestouchsensationisdulledsothatpatientexperiencesnumbnessinhislimbs.

UndesirableeffectsofAutonomicnervoussystem: Bringaboutdecreaseinefficiencies ofurinarybladderleadstoincompleteemptyingofbladderonuncontrollable dribblingofurinewhenblabberCan'tBepitiedcompletely,theretained(or)residualurineharborsdiseasecausingbacteria,whichleadstotheinflammationoftheurinarybladder(cystitis)[44].

Cardiomyopathy: Theassociationofdiabetesmellituswithcardiacdysfunctioncausedbycardiomyopathyintheabsenceofsignificantcoronaryarterydiseasehasbeenrecognizedformanyyearsalthoughitiswell-knownthatdiabeticpatientsaresusceptibletotheeffectsoflargevesselatherosclerosiswithspecificcardiacandcerebralcomplications.
Globally,cardiovasculardiseases(CVD)constituteleadingcauseofmortality.DevelopingcountrieslikeIndiaarealsostrugglingtomanagetheimpactofCVDalongwithgrowingburdenofobesity.Bytheyear2020,itwillaccountforonethirdofthedeaths.Currentprojectionssuggestthatbytheyear2020,Indiawillhavethelargest CVDburdenintheworld.Theprevalenceofthesedisease ismoreinurbanthaninruralareas.LowervitaminCandseleniuminIndiansascomparedtoothergroups,particularlyincombination,couldplayapartintheirincreasedriskofCHD.Thecontinuousincreaseinincidenceofcardiovasculardiseaseisamanifestationofchronicpoordietandlifestylechoices,whichleadtodiabetesandobesity[45].

Animal models of glycosuria

Animal models of Type 1 diabetes mellitus

Type 1 diabetes mellitus in humans is characterized by a specific destruction of the pancreatic β cells, commonly associated with immune-mediated damage. Although the damage may occur silently over many years, at clinical presentation there is little surviving β cell mass and the disorder progresses to absolute insulinopaenia[46-49].

Streptozotocin is a nitrosurea derivative isolated from Streptomyces achromogeneswith broad-spectrum antibiotic and anti-neoplastic activity. It is a powerful alkylating agent that has been shown to interfere with glucose transport, glucokinase function and induce multiple DNA strand breaks. A single large dose of streptozotocin can produce diabetes in rodents, probably as a result of direct toxic effects[50].

Alternatively, multiple small doses of streptozotocin are used (e.g. 40 mg/kg on five consecutive days). In susceptible rodentsthis induces insulinopenic diabetes in which immunedestruction plays a role, as in human Type 1 diabetes.

The multiple low-dose streptozotocin models have been used extensively to study the immunological pathways that lead to insulitis and β cell death. However, the agent will produce diabetes even in the absence of functional T and B cells and, in contrast to the spontaneous animal models

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discussed below, diabetes cannot be reliably transferred to syngenicrecipients by the transfer of splenocytes[51].

The NOD mouse: The NOD mouse was developed by selectively breeding offspring from a laboratory strain that in fact was first used in the study of cataract development (theJcI-ICR mouse). Insulitisis present when the mice are 4–5 weeks old, followed by subclinical β-cell destruction and decreasing circulating insulin concentrations. Frank diabetes typically presents between 12 and 30 weeks of age. Unlike human Type 1 diabetes, ketoacidosis is relatively mild and affected animals can survive for weeks without the administration of insulin.Inbred animals such as the NOD mouse also have benefits when studying other features of diabetes, as genetic heterogeneity need not be considered as a confounding factor. For example, studies have tried to piece together the immunological cascade that includes T-helper type 2 (Th2) cells, effector cells (CD4+, CD8+) and the contribution of cytokines[52-55].

The BB rat: The BB rat was first recognized in the Bio Breeding Laboratories, a commercial breeding company based in Ottawa, in 1974. In diabetes prone strains, weight loss, polyuria, polydipsia, hyperglycaemia and insulinopenia develop at around 12 weeks of age, often at the time of puberty. In common with the human disease, ketoacidosis is severe and fatal unless exogenous insulin is administered. As with the NOD mouse, the pancreatic islets are subjected to an immune attack with T cells, B cells, macrophages and natural killer cells being recruited to the insulitis. A variety of auto-antibodies, including GAD, have been reported in both BB rats and the NOD mouse, although it remains far from clear which, if any, of these are primary autoantigens.BB rat strains prone to diabetes typically have profound Tcelllymphopenia in the circulating blood, specifically lacking T cells that express ART2. Transfusion of histocompatibleT cells expressing ART2 will prevent the spontaneous development of hyperglycaemia in BB rats[56-59].

Prevention of diabetes in NOD mouse and BB rat: Rodent models of Type 1 diabetes have been employed inresearch examining the role of diet (e.g. cow's milk proteins) and a variety of viruses as environmentaltriggers for the disease. For example, infection with the mousehepatitis virus decreases the incidence of diabetes in NODmice, whilst infection with Kilham rat virus increases the riskin BB rats. Immunosupression with cyclosporin in combinationwith other immuno-modulatory compounds such asvitamin D helps prevent diabetes in both BB rats and NODmice. Non-specific immunization with Freund's adjuvantwill also prevent diabetes in these rodent models[60].
Insulin has been administered orally in the hope of inducing tolerance and reducing the immune attack on the pancreatic islets. Some, but not all, studies have shown this strategy can prevent diabetes in the NOD mouse and BB rat. Nicotinamide is known to protect β cells from toxins such as alloxanand also helps prevent the onset of diabetes in NOD mice. As a result of these observations, several trials in humans at high risk of diabetes have been undertaken, including the use of oral insulin and nicotinamide. Unfortunately the results are currently disappointing[61].

Animal models of Type 2 diabetes

Animal models of Type 2 diabetes are likely to be as complex and heterogeneous as the human condition. Advances are most likely to come from interpreting data from several sources. Thus, in some animals, insulin resistance predominates, whilst in others β-cell failure is pre-eminent.

Models where glucose intolerance is part of a wider phenotype of obesity, dyslipidaemia and hypertension may also provide valuable insights into human Type 2 diabetes. As with the NOD mouse and BB rat in Type 1 diabetes, the selective inbreeding of animals that spontaneously develop a Type 2 diabetes-like phenotype has generated many of the strains used today. Much can also be learnt from animals with single gene mutations, as evidenced to by the advances in knowledge generated from the study of the ob/ob, db/db, fa/fa and agouti strains[62-64].

Rodent models of monogenic obesity and diabetes

The GotoKakizaki (GK) rat: The GK rat was developed by the selective breeding of Wistarrats with the highest blood glucose over many generations.The rats develop relatively stable hyperglycaemia in adult life.Typically, the fasting blood glucose is only mildly elevated butrises further on challenge with glucose. Both insulin resistanceand impaired insulin secretion are present. At birth, the GK rathas a reduced number of islets. Inheritance is polygenicand several genome-wide scans have identified

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putativesusceptibility loci on a variety of chromosomes. Incommon with human Type 2 diabetes mellitus, an excess ofmaternal transmission has been reported in some but not allstudies[65,66].

The KK mouse: The original strain of this mouse was bred for large body size. Characteristically, the mouse gradually becomes obese in adult life, associated with insulin resistance, compensatory hyperinsulinaemia and islet cell hyperplasia. Eventually, mild hyperglycaemia supervenes. Food intake is important in determining the severity of the diabetic phenotype and restriction of energy intake reduces both the obesity and hyperglycaemiaseen in this strain of mice. Several different lines have been bred throughout the world and, because of selective breeding and founder effects,these vary both genetically and phenotypically from each other[67].

Reasonsfor using the KK mouse rather than the GK rat include the superiority of the KK mouse in mimicking human obesity (the GK rat being relatively slim) and the generally easier productionof transgenic variants from mice rather than rats. It is important to realize that, in general, one animal model represents only one aspect or subtype of diabetes in humans and care must always be taken when extrapolating results to the clinical setting.

The Nagoya–Shibata–Yasuda (NSY) mouse: As with the KK mouse, this model was developed by selectiveinbreeding, but on this occasion using a laboratory strain ofmouse termed Jc1:ICR (which is also the ancestral strain fromwhich NOD mice were developed). NSY mice spontaneouslydevelop diabetes in an age-dependent manner. The NSY mouse is particularly useful when considering age related phenotypes (e.g. decline in β-cell function). Of interest, a genome-wide linkage scan has identified a sequence variation in the hepatic nuclear factor 1βgene, a gene also implicated in human MODY syndrome[68].

Psammomysobesus (the Israeli sand rat): In its natural habitat, the Israeli sand rat has an essentially vegetariandiet. However, when fed laboratory chow, the animalsbecome obese, insulin resistant and hyperglycaemic. If acholesterol-rich diet is used, hyperlipidaemia and atherosclerosisdevelop. In common with human Type 2 diabetesmellitus, the hyperglycaemic state is associated with an increasein circulating proinsulin and split products presumablybecause of the high demand for insulin secretion driven by insulin resistance. Impaired insulin biosynthesis within theislets has also been reported[66].

The Otsuka Long-Evans Tokushima fatty (OLETF) rat: The OLETF rat originates from an outbred colony of Long-Evans rats selectively bred for glucose intolerance. Therats are mildly obese and, as with NSY mice, males are morelikely to develop diabetes in adult life than females. Genomewidescans have reported susceptibility loci on chromosomes1,7,14 and also the X chromosome. Interestingly,OLETF rats also carry a null allele for the cholecystokinin. Areceptor which may be involved in the regulation of foodintake, however, whether this is causally related to thephenotype is still unclear[64].

Tissue-specific knockouts

Cre is a bacteriophage P1 recombinase enzyme that recognizesspecific sequences of DNA 34-bp long (LoxP sites). When twoof these sites occur close together, Cre will cut out the DNAbetween them. In the laboratory, it is possible to engineer aDNA construct in which Cre is placed next to a tissue-specific promoter. Using the techniquesfor creating transgenic animals outlined above, offspring canbe produced that will have the Cre construct in all their tissues,but it will only be active in sites where the insulin gene promoteris active (i.e. pancreaticβ-cells). A second set of transgenicanimals can be produced that have, for example, theinsulin receptor gene flanked by the target lox P sites[63].

By mating the two animals together, one can develop a line of animals where the insulin receptor gene is only knocked out in pancreatic β-cells. Similarly, animals can be produced that have a gene knocked out in other specific tissues such as liver, adipose tissue or brain[65].

Animal models of diabetes in pregnancy and the role of intrauterine environment

Another important field of diabetes research that has relied heavily on animal experimentation is the study of diabetes in pregnancy and the role of the intrauterine environment on the subsequent development of diabetes amongst offspring.

Firstly, it has been shown that diabetes in pregnancy predisposes to the later development of diabetes amongst offspring. Thus, pups born from rats rendered diabetic by streptozotocintreatment are more likely to become diabetic in adult life than litters born from the same mother before she received the streptozotocin. In embryo transfer experiments, Wistarrats (at low genetic risk of

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diabetes) are more likely to develop hyperglycaemia as adults if they are reared in the uterus of a GotoKakizaki (diabetic) mother than a euglycaemic mother. However, transferring GotoKakizaki embryos into a normal (Wistar) uterus does not seem to reduce their risk of developingdiabetes[62,69].

Secondly, it has been shown that intrauterine malnutrition may also increase the risk of diabetes amongst offspring in later life. This has been achieved by a variety of means, including uterine artery ligation and dietary restriction of pregnant dams. Endocrine pancreas development is altered in fetuses from rats previously showing intrauterine growth retardation in response to malnutrition.

CONCLUSION

Diabetes mellitus (chronic hyperglycemia) can be viewed as an outcome ofthe interplay among the underlying disease process, the environment, and the behavior of the affected individual. Most ofthe efforts ofthe health care team are directed at behaviors such as diet, exercise, and medication, because little can be done at present about the underlying problems and the environment. Thus, at the clinical level, diabetes is a nearly pure example of behavioral medicine. Ultimately, we must cure or prevent diabetes, but for now management of diabetes mellitus is a behavioral art and science.Investigators continue to rely on animal models due to the fact that they can be readily tested, biopsied and autopsied, their genetic and environmental background is already known and generally they serve studies that could not otherwise be accomplished in humans.

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