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Promising Novel Urinary Protein Biomarkers for Assessing Drug Induced Acute Kidney Injury:a Review

KEYWORDS: Biomarkers, acute and chronic kidney damage, omics technology, Kim-1, Timp-1, Osteopontin, Cystatin-C.

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ABSTRACT *Progressionofkidneydiseasefrommildormoderatetoendstagemaybepreventedifitisdetectedataveryearlystage.Sensitivityordiagnosticvaluesofallconventionalbiomarkersarepoor,unreliableandtheirdelayedresponseoftendeliveredfalse-positiveorfalse-negativeresults,whichfinallyleadtoalatedetectionofrenaldamage.Developmentofomicstechnologyleadstotheidentificationofseveralurinaryproteinbiomarkersandtranscriptionalbiomarkerswhichenableearlierdetectionofkidneyinjury.Urinaryproteinbiomarkersshowgoodpredictivepowerandhavegreaterbenefit,becauseofeasyavailabilityofurine.Severalurinaryproteinbiomarkershavebeenidentifiedanddemonstratedsuperiorityindetectingkidneyinjurythanconventionalparameterslikeserumcreatinine(SCr),bloodureanitrogen(BUN),etc.Thesepromisingexperimentalbiomarkersofkidneydamagerequirefurtherconfirmationof their useinroutineclinicaluse.*

Conclusion
Nearlyfor100yearsandstillserumcreatinineisusedasamajordeterminantofkidneyfunction.RIFLEscheme(risk,injury,failure,lossandendstagerenaldiseases)andAKINscheme(acutekidneyinjurynetwork)areoptionsusedforthecclassificationofrenalinjury. Thesemethodsarebasedonthespecificcutoffvaluesofserumcreatinine,GFRorurinaryoutput.DifferentdefinitionsofAKIintheplublishedliteraturesrelyonchangesinSCr.Kidneydisease:improvingglobaloutcome(KDIGO)clinicalpracticeguidelineforAKIrecommendsriskassessmentforallcriticallyillpatients,acknowledgingthatriskassessmentisdifficult.Sothereisanurgentneedforastandarddefinitionwhichisnotbasedonserum Crconcentration.Markersofdamagearebetterthanfunctionalmarkers.

Difficultyinearlyoraccuratedetectionof AKIleadstosignificantproblemsinpatientcareanddrugdevelopment. ThedatageneratedduringpreclinicaltoxicitytestinghastobeasdetailedandinformativeaspossibleasithasbeenobservedthattheincidenceofpatientsinintensivecareunitsdevelopingAKIisabout30-50%,butonly7%ofnewdrugcandidatesfailinthepreclinicaltrialsbecauseoftoxicity(Devarajan,2005).Thisdiscrepancymaybeduetotheunderestimationofnephrotoxicityinpreclinicaltrials.

Functionalgenomicsandproteomicstoolshaveprovidedvariouspromisingnovelbiomarkerswhichwillbeusefulforearlydetectionofdurationandseverityofkidneydiseases.Butnonearecurrentlyestablishedenoughtoreplacecreatinineasamarkerofrenalfunction.

Betterbiomarkerswillhelpdrugdeveloperstotakedecisionsaboutwhichproductstomoveforwardintesting,dosesatwhichtheyshouldbeusedanddesigningclinicaltrialsthatwillprovideclearinformationaboutproductbenefitandsafety.Italsopreventsentryofnephrotoxicdrugsintothemarketandfacilitatesearlymanagementofpatientswhosufferfromkidneyinjury.

Therefore,thesepromisingexperimentalbiomarkersofkidneydamagerequirefurtherconfirmationofitsuseinroutineclinicaluse.

Introduction
Kidneyisoneofthemajororgansevokingdrug-relatedtoxicresponses(Fregusonetal.,2008).Inthepharmaceuticalindustry,-kidneyisoneoftheroutinelyassessedorgansduringpreclinicalsafetyevaluations.

AcuteKidneyInjury(AKI)remainsacommonandseriousclinicalproblemwhichrepresentsanacutedeclineinrenalfunction,finallyleadingtostructuralchanges,associatedwithincreasedmorbidity,mortality,lengthofhospitalstayandcostsinbothsurgicalandmedicalpatients.Ischemia,sepsisandtoxinsarethemostco

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mmonetiologiesinhospitalizedpatients.Drug-inducedkidneydiseaseconstitutesanimportantcauseofacuterenalfailure(ARF)andchronickidneydisease(CKD)inpresentdayclinicalpractice.Drug-inducedARFaccountedfor20%ofallARFinanIndianstudy(Jhaetal., 1995).TheincidenceofmajorriskfactorsofCKDintheworldisincreasingand,itisexpectedthatthisincidenceandprevalence,particularlyindevelopingcountries,willcontinuetoincrease(Najafietal., 2012).Theincidenceofend-stagerenaldisease(ESRD)hasalsodramaticallyincreasingworldwide(Bommeretal.,2002). Anti-cancerdrugs,non-steroidalanti-inflammatorydrugs(NSAIDs),antibiotics,angiotensinconvertingenzyme(ACE)inhibitors,contrastagentsandheavymetalsaremajorculpritdrugscontributorytokidneydamage(Jhaetal.,1995).

Standardparametersinpreclinicalandclinicalstudiesaswellasinroutineclinicalcareforthedetectionandmonitoringofrenalfunctionareserumcreatinine(SCr)andbloodureanitrogen(BUN).Someothertestsmeasureabnormalkidneyfunctionsincludelowered(<60%)glomerularfiltrationrate(GFR),proteinuria,hematuria,highbloodpressure,detectionofurinarycomponentslikeelectrolytes,enzymesandotherwasteproducts.Itisoftenassociatedwithfrequentorpainfulurination,swellingofhandsorinfeetandpuffinessaroundtheeyesetc.

Drug-inducedrenaltoxicityonanimalsystemcanbedirectlyobservedandcharacterizedthroughhistopathologicalobservation,is currentlyconsideredasgoldstandardinpreclinicalstudies.However,itisdifficulttoidentifythetimeatwhichkidneydamageoccurs.Itdoesnotgiveany detailedinformationofnon-histopathologyassociatedtypeofkidneydisturbances.

However,sensitivityordiagnosticvaluesofallofthesepara metersarepoor,unreliableandtheirdelayedresponseoftendeliveredfalse-positiveorfalse-negativeresultswhichfinallyleadtoalatedetectionofrenaldamagefor which dialysisis the only option for treatment.Allofthesesymptomsarenotspecificforkidneydamagebutarealsoreportedforotherorgandamageordiseases.Areductionofrenalfunctionalityoccursonlyaftertwothirdofrenalbiomasshasinjured(Rachedetal.,2008).

Developmentofomicstechnologyleadtotheidentificationofseveralurinaryproteinbiomarkersandtranscriptionalbiomarkerswhichenableearlierdetectionofkidneyinjuryandalsogivesinformationabouttheareaofnephrondamageortheunderlyingmechanism.NovelkidneyinjurybiomarkersinbothserumandurinehavebeendemonstratedsuperiorityindetectingkidneyinjurybeforechangesinconventionalparameterslikeserumcreatinineorBUN.

Urinaryproteinbiomarkershavegreatbenefitofeasyavailabilityofurinesample andlackofsamplepreparationand manyshowinggoodpredictivepower.Enhancedsamplepreparationeffortandlimitationintissueavailabilitylimitstheroutineuseoftranscriptionalbiomarkercomparedtourinaryproteinsbiomarkers.Severalurinaryproteinbiomarkersofnephrotoxicitylike KidneyInjuryMolecule(Kim-I),Clusterin,NeutrophilGelatinaseassociatedLipocalinorLipocalin-2(NGAL/Lcn-2),TissueInhibitorofMetalloproteinases-1(Timp-1),Osteopontin(OPN),Interleukin-18(IL-18),FattyAcidBinding-Protein-LiverType(L-FABP),Vanin,Treffoilfactor-3(TFF-3),etc.,havebeenidentifiedinkidneytissues,serumandinurinebyusingELISA,immunohistochemistryandquantitativerealtimePCRmethods.

Thisreviewisaimedatsheddinglightonsomeofthemostpromisingbiomarkerscurrentlyunderinvestigation,foridentifyingtoxin-mediatedacutekidneyinjury.

Recentreportsonthemostpromisingurinaryproteinbiomarkers

1. KidneyInjuryMolecue-1(KIM-1)

Kim-1isatype-Itransmembraneglycoproteinwithanimmunoglobulin-likedomainconsistingofsixunusualcysteineandalongmucin-likedomaininextracellularregion,localizedtotheapicalmembraneofexclusivelysurvivingproximaltubularepithelialcellsafterinjury(Vaidyaetal.,2008).Itinternalizesapoptoticbodiesandcelldebrisfacilitating,remodelingandregenerationoftubuleepitheliumandthuspreventingtubuleobstructioninresponsetoinjury.Itisexpressedatlowlevelinnormalkidneytissuebutdramaticallyupregulatedandiseasilydetectedintheurineuponnephrotoxicity.

Kim-1hasbeenconsideredasanon-invasivebiomarkerforhumanrenalproximaltubulardamage(Ichimuraetal.,1998).Hoffsmanetal.,2010analyzedthelevelsofKim-1,Lipocalin-2,ClusterinandTimp-1inthekidneyandconfirmedthatKim-1andClusterinareearly,sensitiveandnoninvasivemarkersofrenalinjury,asthemarkersreflectedchangesingene/proteinexpressionandhistopathologicalalterations,inabsenceoffunctionalchanges.Previousstudiesinratsandinpatientswith-AKIdemonstrated,significantlyhighersensitivityandspecificityofurinaryKim-1andClusterin,asmarkersofrenalinjurythantraditionalclinicalchemistryparameters(Etietal.,1993;Hanetal.,2008;Horstrupetal.,2002;Zhouetal.,2008;Vaidhyaetal.,2008).Kim-1isnotdetectedinnormaltissueorurine,buthighlyexpressedinproximaltubularepithelialcellsfollowingtoxicinjury(Vaidyaetal., 2006).AdministrationofOchratoxintomalerratsresultedinadose-time-dependentincreaseinthegeneexpressionofKim-1,Lipocalin-2,Timp-1,OPNandClusterin.InductionofKim-1geneexpressionistheearliestresponsesofthekidneybutnosignificantincreaseingeneexpressionhasbeenseenininvitrostudies(EvaRachedetal.,2008).UrinaryKim-1levelsweresignificantlyelevatedwithin12hafteraristolochicacidadministration,withsignificantincreaseofBUNlevels,onlyonday5,butnochangesinurinaryNAGandtotalproteinweredetectedthroughoutthestudy(Sabbisettietal.,2012).However,urinaryKim-1isreportedtobeincreasedafterthepeaksofurinaryNAGandNGALinpatientswithAKIaftercardiacsurgery(Hanetal.,2009).

2. Lipocalin-2/NeutrophilGelatinaseAssociatedLipocalin/(Lcn-2/NGAL)

Lipocalinsaresmallproteinsthataresentbycellstobindthingsandcarrythemback,mostimportantlipocalinsaresiderophores.Thisfamilyincludesseveralproteinssuchasα1-microglobulin,retinolbindingprotein-4,prostaglandinDsynthaseandnitrophorins,whicharespecializedinbindingandtransportingsmallhydrophobicmolecules.NGAL,alsoknownashumanneutrophillipocalin,lipocalin-2,andsiderocalinbelongstowelldefinedsuperfamilyofproteinscalledlipocalins.NGALisaproteinthatbindstogelatinaseinparticularneutrophilgranulocytesandisupregulatedduringinflammationortumorigenesis(Nielsonetal.,1996)andalsomightbereadilydetectedinurine.NGALmaybeproducedinmanycellsincludingkidneytubule.NGALlevelpredictsthefutureappearanceofAKIaftertreatmentsthat/whichadverselyaffectskidney.Recentevidencealsosuggestsstthatitmaybeinvolvedinpathophysiologicalprocessofchronicrenaldiseasesuchaspolycystickidneydiseaseandglomerulonephritisandhighlyexpressedinmanyotherconditions,likeinfectionorinflammation,includingappendicitis,inflammatorybowelldiseaseorurinarytractinfections,butinclinicalpractice,theinterestisfocusedonAKI.Forallthesereasons,NGALmaybecomeoneofthemostpromisingnext-generationbiomarkersinclinicalnephrology.

NGALwaseasilydetectedinurineofmousewithcisplatin-inducednephrotoxicityprecedingtheappearanceofNAGandβ_2-microglobulin,suggestingasanearly,non-invasivebiomarkerforischemiaandnephrotoxicrenalinjury(Mishraetal.,2003).Inapreviousstudy,theratswereadministeredwithgentamicinandurinaryLcn2wasfoundtobeperformedbetterthankim-1(Seiberetal.,2009).NGAL/lipocalin-2hasbeenrapidlyincreasedandsecretedintourineinarangeofpreclinicalandclinicalstudiesonAKI(Bennettetal.,2008;Nickolasetal.,2008).

PlasmaandurineNGALhaveemergedassensitive,specificandhighlypredictiveearlybiomarkersofAKIaftercardiacsurgeryin

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children,sinceNGALconcentrationincreasedwithin2-6hinpatientswhosubsequentlydevelopedAKIaftersurgery(Waikaret al.,2009).However,ithasbeendemonstratedthaturinaryconcentrationsofLcn2alsoisincreasedinliverfibrosisinducedbycarbontetrachloride(Smythetal.,2008),andelevatedinpatientswithpneumonia(Chanetal.,2009)andinflammatoryboweldisease(Oikonomuetal., 2011).Henceitissuggestedthatitmaynotbespecificforkidneyinjurybutalsooccurinresponsetosystemicinflammationortissuedamageatothersitesororgans.

3. Clusterin

Clusterinisadisulphide-linkedheterodimericglycoproteinconsistingofαandβsubunits(JonesandJomary,2000;Kujiraokaetal.,2004),presentinthecytoplasmofproximalconvolutedtubuleorattheendofdistalconvolutedtubule(DCT)includingconnectingtubuleinthekidneycortex.Clusterin,anapolipoproteinwhensecreted,protectscellsagainstapoptosisandcytolysisbycomplementandassociateswithmembranerecycling,lipidtransportation,tissueremodeling,spermmaturation,etc(Julyetal.,2002).Itcanbeusedasapotentialmarkerofnephrotoxicity,sinceitisupregulatedanddetectedintheurineofpatientswithAKI.Ithasbeenconfirmedthatthedepletionofclusterinworsensglomerulonephritis(Kharashetal., 2006).

Increasedexpressionofclusterinwasfoundintubulesshowingsignsofcelldeathandregeneration,indicatingitsroleintissueremodelingafterdamage(Rosenbergetal.,1995).Clusterinhasbeenimplicatedinapoptosisandgrowthcontrol,celladhesionandtissueremodelingandsignificantlyupregulatedinresponsetocellularstress(Shannanetal.,2006).Reductionofinducibleexpressionofclusterinresultsinanincreaseinrenaltubularepithelialcellapoptosisintheculturesandrendersmicemoresusceptibletoischaemic-reperfusioninjury,showingaprotectiveroleofclusterininkidneyinjury(WenjunZhouetal., 2010).ExpressionofclusterinmRNAwassignificantlyincreasedwithin6hinratunilateralureteralobstructionmodelandsuggestedthatdetectionofclusterinmRNAandclusterin-βinthekidneyorclusterin–αintheurinemaybeusefulforpredictingnephrotoxicity(Ishiletal.,2007).Clusterinhassignificantlyincreasedinpatientswithbladdercancerraisingtheconcernthatthepresenceofclusterinmaynotbelinkedonlytokidneytoxicity(StejskalandFiala,2006).

4. Interleukin-18(IL-18)

IL-18isawidelyexpressedpro-inflammatorycytokine,formerlyknownasinterferon-gamma-inducingfactor,producedbyrenaltubularcellsandbymacrophages.IL-18inducesinterferon-gammaproductioninTcellsandnaturalkillercellsandhasanactiveroleinapoptosis,ischemia,infection,malignancyandautoimmunecondition(Melnikovetal.,2001).

Johnetal.,2013,measuredtheconcentrationofIL-18inurinesamplesof95patientswithAKIaftercardiacsurgeryandfoundIL-18wasthebestpredictor,inadditiontoL-FABP,NGALandKIM-1,whichwerealsogoodpredictors.Liuetal.,2013foundIL-18asausefulbiomarkerofAKIwithmoderatepredictivevalueacrossallclinicalsettings.Inacrosssectionalstudy,urineIL-18levelsweremarkedlyelevatedinpatientswithestablishedAKI,butnotinsubjectswithUTI,CKDandnephroticsyndrome(Parikhetal.,2004).UrinaryIL-18wassignificantlyupregulatedinpatientswithacuterespiratorydistresssyndromewhodevelopedAKI(Parikhetal.,2005).UrinaryIL-18levelwassignificantlyelevatedwithin6hinchildrenundergoingcardiopulmonarybypass(CPB)whodevelopedAKI,(Parikhetal.,2006).IL-18isapredictivebiomarkerinkidneytransplantation(Parikhetal.,2006).Overall,IL-18appearstobemorespecifictoAKIandhasbeenanticipatedasapossibleearlymarker.

5. Vanin-1

Vainin-1isanepithelialectoenzymewithpantetheinaseactivity,whichcatalyzestheconversionofpantetheineintopantothenicacidandcysteamine.Lackofcysteamineisassociatedwithenhancedy-glutamylcysteinesynthetaseactivityleadingtoelevationofendogenousglutathionestoresintissueswhichprotecttissueagainstthedegeneratingeffectsofoxidativedamagebyscavengingfreeradicals(MeisterandAnderson,1983).Higherserumandurinaryconcentrationsof Vanin-1wereobservedinethyleneglycoltreatedgroupscomparedtocontrolgroup,suggestingitasausefulandrapidbiomarkerforrenaltubularinjury(Hosohataetal.,2011).

Arecentstudyhasbeenconductedtodeterminewhetherincreaseinurinaryvaninisdetectedbeforetheelevationsofserumcreatinine,urinaryNAG,Kim-1,andNGALinanimalmodelsinducednephrotoxicitybycisplatinandgentamicin.Uriniaryvanin-1wasdetectedearlierthananyotherbiomarkersaftertheadministrationofhigherdosesofbothdrugs.Thisresultsuggestedthat,comparedwithurinaryKim-1andNGAL,urinaryvanin-1isanearlierandequallysensitivebiomarkerfordruginducedAKI(KeikoHosohataetal.,2012).UrinaryVanin-1wasincreasedinpatientswithdiabeticnephropathy(Fugmannetal.,2011)andproteinlevelsofrenalvanin-1wasincreasedinratswithstreptozotocin-induceddiabeticnephropathy.Therefore,itisanticipatedthaturinaryvanin-1isapotentialbiomarkerofearlydetectionofAKI.

6. Treffoilfactor3(TFF3)

Treffoilfactorsaremultifunctionalpeptides,mainlyexpressedinalimentarycanalandprotectitfromthedegradativeeffectofHCl,bystimulatinggobletcellstosynthesizemucin.Downregulationoftrefoilfactor3maycontributetoincreasedagerelatedtissuedamagetothekidney.TFF3mayplaykeyrolesinregenerationandinongoingrepairofkidneydamage(Astoretal.,2011).

UrinaryTFF3andalbuminenabledmoresensitivemarkersfordiagnosisofacuterenaltubularinjurythantraditionalmarkers(Yuetal.,2010).Acasecontrolstudythatwasperformedover8.6yearsfoundthathigherurinaryTFF3wereassociatedwithCKD,maybeausefulmarkerinfuturestudies(Astoretal.,2011).ExpressionofTFF3invivoiscorrelatedwithinflammationofgastrointestinaltract,andavarietyofsolidcancers(Khouryetal.,2005).Thesestudyreportsindicatethatitmaynotbeaspecificindicatorforacutekidneytoxicity.

7. Insulinlikegrowthfactorbindingprotein-7(IGFBP7)

IGFBP7involvedinG1cellcyclearrestduringearlyphaseofcellinjuryandmaypreventthecelldivisionwithdamagedDNA,untilDNAdamageisrepaired(Rodieretal.,2007;Boonstraetal.,2004).

PreviousstudyinvestigatedtheconcentrationofurinaryIGFBP7andTimp-1in50patientsundergoingcardiacsurgeryandresultsindicatedthatbothservedassensitiveandspecificbiomarkertopredictAKIearly,aftercardiacsurgeryandtopredictrenalrecovery.AUClevelwassignificantlyhigherforIGFBP7andTimp-1,i.e.,superiortootherbiomarkerslikeKim-1,NGAL,cystatinC,IL-18topredictAKI(Mishraetal.,2003;Koyneretal.,2008;Hanetal.,2002).

8. TissueInhibitorofmetalloproteinase-1(Timp-1).

Timp-1isanendogenous,specificinhibitorofmatrixmetalloproteinases(MMPs)byforminghighaffinitycomplexesandthereby-blockingbindingofMMPstothesubstrate.MMPs,belongedtoafamilyofproteolyticenzymesthatdegradevarioustypesofextracellularmatrixcomponents(ECM).Timp-1promotesrenalfibrosisthroughinhibitionofmatrixmetalloproteinaseandaccumulationofcollagen.DownregulationofMMPsandupregulationofTIMPsleadtoaccumulationofECMproteinsandprogressionofCRF,whicharecharacterizedbytubulointerstitialfibrosisandglomerulosclerosis(Lenzetal.,2000).ItalsoinvolvedinG1cellcyclearrest.Previousstudiesreportedincreasedurinaryexcretionof Timp-1inpatientswithrenaldisease.

PreviousstudydemonstratedthattheprotectiveroleofMMP-9inCRFwasbydegradingECMorthroughthesuppressionofTimp-1andtheproinflammatoryresponse(Leiwangetal.,2013).EnhancedurinaryexcretionofTimp-1wasseeninhighdoseanimals(Hoffsmanetal.,2010)buttheoverallperformanceofTimp-1asanearlyindicatorofproximaltubularinjurywaspoor,comparedtoKim-1andclusterin.ElevatedlevelsofTimp-1havebeenobservedinmodelsofkidneyinjuryandinurineofpatientswithrenaldiseasesascomparedtohealthycontrols(WasilewsaandZoch-Zwierz,2008).Recentevidencesuggeststhat Timp-1increasesgranulocyteduringinfla

mmation(Chormeketal.,2004).Timp-1andclusterinwerefoundtobelesssensitivethankim-1andlipocalin(Maxetal.,2009).

9. Liver-typeFattyacidBindingProtein(L-FABP)
L-FABPsaresmallcytoplasmaticproteinsabundantlyexpressedmainlyinproximaltubuleofkidneyandalsointissueswithactivefattyacidmetabolism.Primaryfunctionofthisproteinisthefacilitationoflongchainfattyacidtransport.

Increasedurinaryexpressionshavebeendescribedinanimalmodelsof AKI(Noirietal.,2009;Yamamotoetal.,2007;Negishietal.,2009).Inhospitalizedpatientswithestablished AKI, theAUCofurinaryL-FABPforpredictionofAKIwas0.97,whichigherinpatientswithpooroutcome(Fergusonetal.,2010).Inpatientswithsepticshockand AKI,urinaryL-FABPlevelswere significantlyhigher(DoiKetal.,2010)andalsoincreasedinCKD(Kamijoetal.,2006).UrinaryL-typefattyacidbindingproteinwasshowntoincreasewithin2hofcisplatinadministrationandcorrelatedwithhistologicalinjuryscorethanBUN(Negishietal.,2009),indicatingL-FABPasapromisingandsensitivebiomarkerthanKim.

10.Osteopontin(OPN)
Osteopontin,abonephosphoprotein,isamultifunctionalproteinsecretedbyvarietyofcelltypesandisinvolvedindiversebiologicprocessesincludinginflammation,leukocyterecruitment,woundhealing,and cellsurvivalandalsoinbiologiccalcification. ItisalsoknownassialoproteinI,secretedphosphoproteinI,uropontinandearlyT-lymphocyteactivation-1(Eta-1)(Oldbergetal.,1986;Nomuraetal.,1988;Patarcaetal.,1989;Shiragaetal.,1992). OPNissynthesizedwithinkidneyandispresentinhumanurineatlevelsthatcaneffectivelyinhibitCaOxcrystallization(Minetal., 1998;Asplinetal.,1998).

Itisexpressedmosthighlyinepithelialtissueandbone,andcanbedetectedatahighlevelinhumanurinewhenthekidneyissignificantlydamagedbygentamicin,cisplatin,cyclosporin,sevoflurane,angiotensionII-inducedtubulointerstitialnephritis,andpuromycin-inducedglomerulonephritis(Alchietal.,2005).Studiesdemonstratedthatincreaseurinarylevelsof OPN,inchildrenwithsteroid-resistantnephroticsyndromeaswellasinmicesufferingfromfocalsegmentalglomerulosclerosis, indicatedasapromisingkidneymarker(Lorenzenetal.,2008;Shuietal.,2007).

11.Renalpapillaryantigen(RPA-1)
RPA-1isacollectingduct-specificproteinofhighmolecularweightglycoprotein,andtheactualepitoperecognizedbytheRPA-1antibodyislikelytobecarbohydrateinnature,formingpartofanN-linkedglycoprotein.

Gentamicinandchromiumtreatedratsexhibitedincreasedimmunoreactivityof RPA-1,RPA-2,Kim-1largelyintheS1/S2segmentsandtoalesserextentintheS3segmentsoftheproximaltubuleofkidney,whereasmercury(Hg)treatedratsshowedincreasedimmunoreactivityofKim-1,RPA-1,RPA-2intheS3segments.Theseproteinsweremoreabundantininjured,necrotic,andapoptoticcellsofS1/S2andS3segmentsthaninthenormalhealthyrats(JunZhangetal.,2008).

12.Hepatocytegrowthfactor(HGF)
Hepatocytegrowthfactor,isapleiotrophicfactororiginallyisolatedasapotentmitogenforhepatocytesandplaysanimportantroleintissuerepairandregenerationafterinjury.Expressionofboth-HGFanditsc-metreceptorgenesisrapidlyupregulatedafter AKI.

AdministrationofexogenousHGFnotonlypromotesrenaltubularrepairafterinjurybutalsofunctions ascytoprotectiveagentbyprotectingtubularepithelialcellsagainstbothapoptoticandnecroticdeath(ChunsunDetal.,2001).Vishaletal.,2008evaluatedthediagnosticperformanceof9urinaryproteinbiomarkersof AKIincludingKIM-1,IL-18,HGF,CystatinC,NGAL,NAG,VEGF,chemokineinterferon-inducibleprotein(IP-10)andtotalproteininacrosssectionalcomparisonof204patientsandconfirmedthatKIM-1,NGAL,HGFandtotalproteinwerethefourbestperformer sindividuallyandincombinations.

13.Cystatin-C
Cystatin-Cisanon-glycosylatedextracellularcysteineprotease inhibitorandapotentinhibitoroflysosomalproteinases,andmainlyusedasbiomarkerofkidneyfunction.Cystatin-CisfoundinCSFandurineofpatientswithrenalfailure.IfkidneyfunctionandGFRdeclines,thebloodlevelofCystatin-Crises.Cystatin-Cislessdependentonage,sex,raceandmusclemasscomparedtocreatinine.

Kim-1,Cystatin-C,TIMP-1,andosteopontinmayserveaspromisingnoninvasiveurinarybiomarkersforearlierdetectionandmonitoringofrenalinjurycomparedtootherbiomarkerslikebeta-2-microglobulin,α-GST,VEGF,calbindin,clusterin,NGAL,OPN,BUNandSCrinkidneytoxicityinducedratmodels(Mihyeetal.,2012).Cystatinlevelshavebeenreportedtobealteredinpatientswithcancer(Kosetal.,1998),thyroiddysfunction(FrickerMetal.,2003),HIVinfection(Oddenetal.,2007),cardiovasculardiseases,andbraindisorderslikeAlzheimer'sdisease.

14.TypeIVcollagen
TypeIVcollagen,amaincomponentofthebasementmembrane,increasesintheurinefollowingdamageoftheglomerulus.Becauseitistoolargetopassthroughtheoutermembraneoftheglomerulus,itsconcentrationintheurineisasensitiveindicatorforglomerularchangesinthestructureoftheextracellularmatrixandthusanimportantbiomarkerofnephrotoxicity(Donovanetal.,1994)

Inadditiontotheaforementionedurinaryproteinbiomarkers,variouscytokineslikeinterferon,tumournecrosisfactor,colonystimulatingfactorandseveralgrowthfactorsactasmediatorsofinflammationandimmuneresponsesandasbiomarkerofnephrotoxicity,becausetheyareinvolvedintubulardamageandrepair.

FutureProspects
Futurestudiesarerequired

i). Tovalidatethesensitivityandspecificityofthesemarkersinclinicalsamplesfromlargecohortsandinmultipleclinicalsituations,
ii). Tounderstandtheperformanceofthesebiomarkersinothertypesofrenalinjury,
iii). Toelucidatewhycertainnephronsegmentsareaffectedbycertaintoxicantsandnotbyothersandthismayhelptoidentifymechanismoftoxicactionandaidthesearchforsitespecificbiomarkers.
iv). Todateonlylimiteddataareavailableregardinggenderdifferenceindruginducedrenalinjury.

ResearchstudiesfocusingonlyonKim-1,wouldbewrongasitindicatestherenaldamageonlyonS3segments(RosenandHaymen,2003).Recentreportsalsoindicatethatotherbiomarkerslike IL-18,IGFBPandVaninaremoresensitivethanKim-1.

Conclusion
Nearlyfor100yearsandstillserumcreatinineisusedasamajordeterminantofkidneyfunction.RIFLEscheme(risk,injury,failure,lossandendstagerenaldiseases)and AKINscheme(acutekidneyinjurynetwork)areoptionsusedfortheclassificationofrenalinjury. Thesemethodsarebasedonthespecificcutoffvaluesofserumcreatinine,GFRorurinaryoutput.DifferentdefinitionsofAKIinthepublishedliteraturesrelyonchangesinSCr.Kidneydisease:improvingglobaloutcome(KDIGO)clinicalpracticeguidelinefor AKIrecommendsriskassessmentforallcriticallyillpatients,acknowledgingthatriskassessmentisdifficult.Sothereisanurgentneedforastandarddefinitionwhichisnotbasedonserum Crconcentration.Markersofdamagearebetterthanfunctionalmarkers.

Difficultyinearlyoraccuratedetection of AKIleadstosignificantproblemsinpatientcareanddrugdevelopment. Thedatagenerateddurингpreclinicaltoxicitytestinghastobeasdetailedandinformativeaspossibleasithasbeenob-

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servedthattheincidenceofpatientsinintensivecareunitsdevelopingAKIisabout30-50%,butonly7%ofnewdrugcandidatesfailinthepreclinicaltrialsbecauseoftoxicity(Devarajan,2005).Thisdiscrepancymaybeduetotheunderestimationofnephrotoxicityinpreclinicaltrials.

Functionalgenomicsandproteomicstoolshaveprovidedvariouspromisingnovelbiomarkerswhichwillbeusefulforearlydetectionofdurationandseverityofkidneydiseases.Butnoneare currentlyestablishedenoughtoreplacecreatinineasamarkerofrenalfunction.

Betterbiomarkerswillhelpdrugdeveloperstotakedecisionsaboutwhichproductstomoveforwardintesting,dosesatwhichtheyshouldbeusedanddesigningclinicaltrialsthatwillprovideclearinformationaboutproductbenefitandsafety.Italsopreventsentryofnephrotoxicdrugsintothemarketandfacilitatesearlymanagementofpatientswhosufferfromkidneyinjury.

Therefore,thesepromisingexperimentalbiomarkersofkidneydamagerequirefurtherconfirmationofitsuseinroutineclinicaluse.

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