Apoptosis & diabetes mellitus

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Diabetes mellitusDiabetes mellitus is a group of metabolic diseases characterized byhyperglycemia resulting from defects of insulin secretion and/or increasedcellular resistance to insulin.Diabetes mellitus is classified into type 1, type 2, gestational and otherspecific typesManifested by polyuria, polydepsia and polyphagia.Diagnosed byFPG ≥126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes.2-h post load glucose ≥200 mg/dl = provisional diagnosis of diabetes.Symptoms of hyperglycemia and casual plasma glucose ≥ (200 mg/dL).Glycated hemoglobin (Hb A1C) ≥ 6.5%.Screening is recommended to obese, hypertensive,family history of diabetesor gestational diabetes and dyslipidemia.Complications of diabetes include acute complications as DKA, HONK andhypoglycemia. and chronic complications in form of microangiopathy as144retinopathy, nephropathy and neuropathy. and macroangiopathy as coronaryheart disease strokes and peripheral arterial disease.Treatment of diabetes includes:1- Patient education about the disease nature and ideal food andpossible complications.2- Diet patient should be educated about ideal food weight control.3- Exercise has beneficial effects for diabetics and good glycemiccontrol.4- Oral drugs include biguanides as metformin which isrecommended in all type 2 diabetics but has high incidence ofGIT complaint. And sulphonylureas which is potent drugs withmore incidence of hypoglycemia. Also TZDs which is goodoption in treatment. And alpha glucosidase inhibitors but it is aweak drugs can be combined with any other medications. Withnew drugs GLP 1 analogue and DPP4 inhibitors which isexcellent drugs with high safety profile but expensive. Oraldrugs can be combined with insulin if oral drugs failed alone.5- Insulin therapy which is the treatment of type 1 and some casesof type 2 diabetes insulin has several preparations in marketwith several treatment regimens for easy control ofhyperglycemia.ApoptosisApoptosis is the process of Programmed cell death.145The alternative to apoptotic cell death is necrosis, which is considered to bea toxic process where the cell is a passive victim and follows an energyindependentmode of death.There is many differences between apoptosis and necrosis regardingprovoking stimuli, morphologic changes, inflammatory response, cell fateand molecular changes.Apoptosis activation occurs through caspases or caspase independentCaspase activation occurs through 3 ways they are the death receptor(extrinsic) and mitochondrial (intrinsic), and the third is an intrinsic pathwayinvolving the endoplasmic reticulum.The caspases involved in apoptosis are subdivided into initiator caspases (2,8, 9, 10) and effector caspases.Apoptosis manifests in two major execution programs downstream of thedeath signal: the

caspase pathway and organelle dysfunction.When caspases activated caspase cascade runs end with execution of thecell.Granzyme B: There is an accessory method of triggering apoptosis by theserine protease granzyme BApoptosis is regulated by proapoptotic mediators which cause positiveinduction and antiapoptotic mediators which cause negative inductionRegulators of mitochondrial apoptosis are Apoptosis-relevant proteins of the146OMM are the VDAC and Bcl-2 members. The adenine nucleosidetranslocator is situated in the IMM.Activation of the pro-apoptotic molecule BAX appears to involvesubcellular translocation and dimerization.The BH3-domain BIM also translocates to the mitochondria followingcertain apoptotic stimuli.the BH3-domain-only molecule BAD is phosphorylated on two serine sites.Following TNFα or Fas treatment, BID, a BH3-domain-only molecule iscleaved at its amino terminus.Abnormalities in cell death regulation can be a significantcomponent of diseases such as cancer, autoimmune lymphoproliferativesyndrome, AIDS, ischemia, and neurodegenerative diseases such asParkinson’s disease, Alzheimer’s disease, Huntington’s disease, andAmyotrophic Lateral Sclerosis. Some conditions feature insufficientapoptosis whereas others feature excessive apoptosis.potential methods of anti-apoptotic therapy includes stimulation of the IAP(inhibitors of apoptosis proteins) family of proteins, caspase inhibition,PARP (poly [ADP-ribose] polymerase) inhibition, stimulation of thePKB/Akt (protein kinase B) pathway, and inhibition of Bcl-2 proteins.147Apoptosis assays can be classified into Cytomorphological alterations,DNA fragmentation, Detection of caspases, cleaved substrates, regulatorsand inhibitors, Membrane alterations, Detection of apoptosis in wholemounts and Mitochondrial assays.Apoptosis & diabetes mellitusDiabetes mellitus is one of the most common non-communicable diseases.Pancreatic B-cell loss by apoptosis appears to play an important role in thedevelopment of insulin deficiency and the onset and/or progression of thedisease.β-Cell apoptosis is a key event contributing to the pathogenesis of type 1diabetes mellitus.induction of B-cell apoptosis by death receptors through studies in type 1diabetes As a result, macrophages and cytotoxic T lymphocytes have beenaccused of dealing the lethal blow to B-cells Studies from autopsies ofsubjects affected by Type 2 diabetes demonstrated that in some, although notall individuals with diabetes, there is a marked decrease in beta cells massfree fatty acids, glucose, sulfonylurea, and the islet cell hormone termedamylin can cause beta-cell apoptosis. This suggests that PCD may also beinvolved in the pathogenesis of Type 2 diabetes.New and convincing data indicating that increased apoptosis rather thandecreased neogenesis or replication may be the main mechanism leading toreduced B-cell mass in type 2 diabetics.148Cytokines, lipotoxity, and glucotoxity are three main stimuli for beta-cellapoptosis.Replication of somatic cells including B-cells occurs at a limited rate inadulthood, B-cell apoptotic death is likely to occur at a slow rate, which iscompatible with the slow development of diabetes.(GLP-1) has recently been found to have antiapoptotic properties. This newproperty of GLP-1 has clinical relevance for the treatment of patients withovert DM, possible prevention of DM during the stage of impaired glucosetolerance.In both animal models and in Type 2 diabetes patients Imatinib seems toimprove glycemic control, possibly via an insulin sensitizing effect.B-cell death is a common event in MODY.Renal apoptosis in

diabetic nephropathy are scarce and scattered, but boththe intrinsic and extrinsic apoptotic pathway seems to be involved.Diabetes causes apoptosis of neural and vascular cells in the retina.Apoptosis plays an important role in the healing process, Apoptosis ofmatrix-producing cells at this stage may interfere with the ability to produceenough matrix and limit repair.149Cardiomyocyte apoptosis causes a loss of contractile units which reducesorgan function and provokes cardiac remodeling which increase incidence ofheart failure.New strategies to prevent B cell apoptosis include: (1) to remove stimulifrom the islet and keep it in a safety environment; (2) to attenuate theapoptotic stimuli and stop the apoptosis at an early stage; (3) to block thepathway of apoptosis and stop the process; (4) to change the balancebetween pro and anti-apoptosis and reverse the cellular apoptotic process.