Effect of Uric Acid on Blood Glucose Levels

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ABSTRAK

Asam urat sebagai hasil akhir dari metabolisme purin basa. Dalam kondisi tingkat tinggi, asam urat memasuki sel dan bertindak sebagai oksidan, kemudian bertindak sebagai faktor risiko independen dan memprediksi kejadian diabetes melitus tipe 2 (T2DM). Ini dapat langsung menonaktifkan atau melalui reaksi oksidatif yang menurunkan tingkat oksida nitrat (NO). Level NO yang lebih rendah akan mengurangi penyerapan insulin dalam jaringan dan mengurangi translokasi GLUT4 dalam sel yang akan mempengaruhi kadar gula darah. Tingginya kadar asam urat atau hyperuricemia membuat stres oksidatif dengan menginduksi produksi spesies oksigen reaktif (ROS) yang mengganggu jalur persinyalan insulin, menciptakan keadaan peradangan yang mengurangi sensitivitas insulin, serapan glukosa darah dan metabolisme, juga mengurangi produksi insulin dari sel islet pankreas.

Kata kunci: *kadar asam urat, nitric oxide (NO), stres oksidatif, gula darah.*

ABSTRACT

Uric acid as the final result of purine bases metabolism. In high level condition, uric acid enters the cell and act as oxidant, and acts as independent risk factor and predicts the incident of type 2 diabetes mellitus (T2DM). It may directly inactivate or through oxidative reaction that lower the nitric oxide (NO) level. Lower NO level will reduce insulin uptake in tissues and reduce in GLUT4 translocation in cell that will effect the blood glucose level. The High level of uric acid or hyperuricemia makes oxidative stress by inducing the production of reactive oxygen species (ROS) which interferes the insulin signalling pathway,creates inflammatory state that reduced the insulin sensitivity,blood glucose uptake and metabolism, also reducing the insulin production from pancreatic islet cells.

Keywords: *uric acid levels, nitric oxide (NO), oxidative stress, blood glucose.*

INTRODUCTION

Uric acid is a diprotic acid a result of final breakdown product of purine bases metabolism. Normal reference of uric acif in human blood is 1.5-6 mg/dL in women and 2.5-7 mg/dL in men. Outside cell environment, it acts as antioxidant, scavenging oxygen peroxyl or ROS and hydroxyl (OH) radicals.[1-3] Several evidences from epidemiological studies that serum uric acid level is an idependent risk factor and predicts a 17% increment in the risk of T2DM.[3-4] Insulin can stimulate the urate-anion exchanger in the brush border membranes of renal proximal tubules and raise the renal urate reabsorption. This proccess makes the serum uric acid levels increased along with increase level of blood

glucose levels reflected on the glycohaemoglobin levels (HbA1C) less than 7% but then decresed with further increament of HbA1C level more than 7%, and it makes a bell-shape relation.[5]

High level, uric acid enters cell through specific anion transporters, inducing oxidative streess by stimulating nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) which results in increased production of ROS, and direct inactivation of NO.[3] Uric acid is reported to induce insulin resistance. One of the theory, it may reduce the bioavailability of NO, which is important for insulin-stimulated glucose uptake in skeletal muscles, and also induces inflammation.[6]

URIC ACID'S EFFECTS ON NITRIC OXIDE AND BLOOD GLUCOSE

Nitric oxide at low dose may promote insulin uptake since it causes dilatation of both resistant and terminal arterioles in skeletal muscle in vivo. Increased concentration of uric acid may cause direct inactivation of NO by changing it into 6-aminouracil, and reduced the insulin uptake.[7] Nitric oxide may induce the cyclic guanosine mono phosphate (cGMP) formation using granulate cyclase, increasing glucose uptake (cGMP-dependent pathway). The formation of cGMP may activate protein kinase G (PKG). The activation of PKG is likely to be associated with GLUT4 translocation which is raising the glucose uptake. The reduction in NO level by ROS produced by uric acid condition will reduce the GLUT4 translocation and the glucose uptake.[8] (**Figure 1**)

The ROS as well as peroxynitrite (ONOO) producing a reaction between superoxide anion (O_2-) with NO, inducing degradation of the cofactor of nitric oxyde synthase (NOS), tetrahydrobiopterin (BH4), causes uncoupling of endothelial NOS then reduce the bioavailability of NO. Peroxynitrite is an oxidant that oxidizes lipids, proteins, nitrated amino acids and DNA.[9-11]

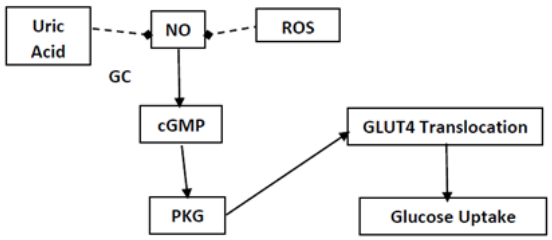

Figure 1. Nitric oxide increases GLUT4 translocation and glucose uptake. Uric acid may directly change NO into inactive form. ROS may degradate the cofactor of NOS, reducing NO bioavailability.

OXIDATIVE STRESS CAUSED BY URIC ACID AND ITS EFFECT ON BLOOD GLUCOSE

Uric acid may disturb the glucose and insulin tolerances through oxidative stress by inducing ROS production through NADPH oxidase stimulation.[4] Xanthine oxidase in the formation of uric acid may also produce ROS. Uric acid directly increased the phosphorylated insulin receptor substrate 1 (IRS1, Ser307) and phospho-Akt (Ser473),inducing insulin resistance.[12] Uric acid may activate NADPH oxidase to produce ROS, consists of O2- dan hydrogen peroxide (H2O2).[4,13] All protein tyrosine phosphatases share a common structure with a catalytically essential cyctein residue in the active centre that has catalytic activity. It may be inactivated either by reaction with H_2O_2 into sulfenic acid derivative or by reaction with glutathione disulfide through glutathiolation proccess of critical cystein residue.[13] The ROS may attenuate insulin signaling,involving the redox-sensitive and insensitive serine kinases (SerKs) by reducing IRS1 signalling to phosphatidylinositol 3 kinase (PI3K).[14]

The ROS may also activate redox-dependent activation of the proinflammatory signalling through p38 mitogen activated protein (MAP) kinase and nuclear transcription factor, nuclear factor kappa-beta (NF-κβ) and activator protein-1 (AP-1) as transcription factor, then followed by the increase production of monocyte chemoattractant protein-1 (MCP-1), and may induce apoptosis.[14-15] The MCP-1 has an important role in the recruitment of monocytes contributing in initiation and inflammation reactions.

Uric acid may also induce mononuclear cells to produced interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), but the most important pro-inflammatory mediators involved in inflammation are IL-6

and TNF-α.[15-16] The IL-6 activates Src (proto-oncogene tyrosine-protein kinase)-homology 2 domain (SH2)-containing: SHP-2, and signal transducer and activator of transcription 3 (STAT3) resulting in increased expression of cytokine signalling 3 (SOCS3). The IL-6 also activate several serine/threonine kinases such c-Jun N-terminal kinases (JNK), p38MAPK, and PKC-δ wich contributes in reducing insulin sensitivity and glucose metabolism. The TNF-α causes insulin resistance by suppressing IRS-1 associated insulin signalling and glucose transport in skeletal muscle.[16]

Uric Acid may stimulate receptor for advanced glycation end products (RAGE) as a transmembrane multiligand receptor of the immunoglobulin superfamily which has been implicated in many chronic diseases and also inflammation. After the RAGE signaling pathway is stimulated, then the NF-κβ will be activated, resulting in the production and release of pro-inflammatory cytokines, and also increasing the expression and extracellular release of high mobility group box chromosomal protein 1 (HMGB1) that causes the amplification of inflammatory response.[17] (**Figure 2**)

Uric acid also may decrease glucose-stimulated insulin secretion from pancreatic islet cells. Insulin biosynthesis is regulated by two main transcription factors, pancreatic and duodenal homeobox-1 (PDX-1) and mafA which bind to their promoter region. It is known that p38 MAPK and JNK which are activated by ROS, are also available in pancreatic islet cells and the amount and activity of c-Jun phosphorylated by JNK are also raise in number by ROS. The c-Jun may interfere the insulin transcription proccess at the promotor region by translocating PDX-1 from nucleus into cytoplasm and decrease of posttranslational mafA protein level.[18] The mafA is also degradated using proteosomal system and it is enhanced in the uric acid-treated cells, and makes the decreased of insulin gene expression,insulin production, and insulin secretion.[19] (**Figure 3**)

CONCLUSION

Uric acid may have an effect on blood glucose levels, disturbing glucose metabolism and also insulin sensitivity and production. In hyperuricemia,uric acid may enter the cells and becomes oxidant. It may reduce the bioavailability of NO, as the result there are a reduction the in synthesis, inactivation, including reduced the translocation of GLUT4. The hyperuricemia condition may induce

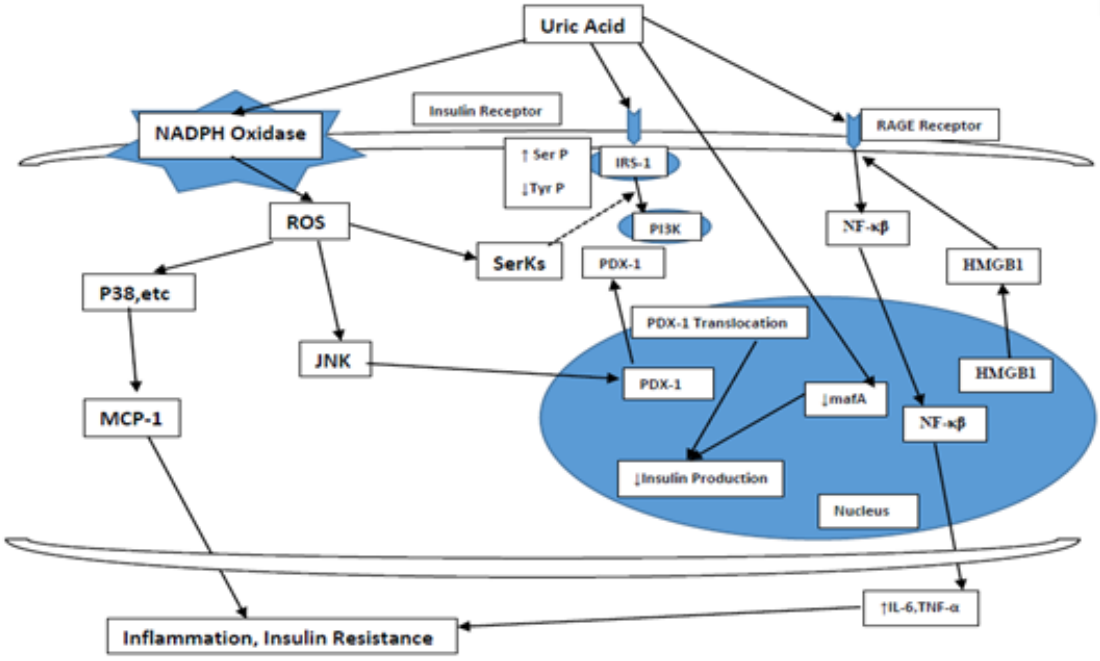

Figure 2. Uric acid is causing oxidative stress and reducing insulin production,secretion, and sensitivity.

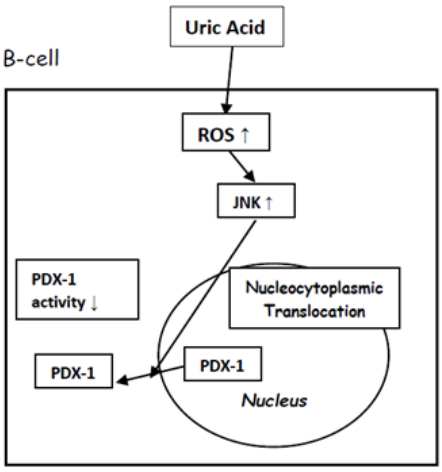

Figure 3. Uric acid inducing ROS formation, inducing JNK activation and PDX-1 translocation.

oxidative stress that disturbing the insulin signalling pathway, inducing inflammation with insulin resistance as the result, also reducing the production and secretion of insulin.

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