Future of Metformin Administration in Sepsis Management

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Sepsis as the host responsive syndrome is one of the main concerning issues and costly disease on intensive care unit (ICU) in the 21st century. Epidemiological studies have showed that mortality rates of sepsis in ICU and hospitals among 37 countries were 39.2% and 49.6% respectively [1]. Complicated nature of sepsis is still not well understood and this makes it hard to treat and manage. According to the failure of current therapies in the management of sepsis and the emergence of antibiotic resistant bacterial strains, new pharmaceutical approaches are needed to trigger precise molecular pathways in septic patients [2].

Metformin (1,1 dimethyl hydrochloride) is a unique member of biguanide family and approved as an anti-diabetic product with minimal adverse effects. Beyond the conventional role of metformin in medication for type 2 diabetes (T2DM) [3], it has been shown that metformin has anti-cancer possession [4] obese adolescent's treatment [5], decreased risk of cardiovascular disease [6-7], inflammation recovery in burned subjects [8], antioxidant and anti oxidative stress traits [9], protection against hypertension and polycystic ovary syndrome(PCOS) improvement [10]. Despite its valuable properties, many controversies exist on its administration in septic subjects. The rising lactate level has a pivotal role in sepsis initiation, on the contrary inhibitory effects of metformin on complex I of mitochondria cause metformin associated lactic acidosis (MALA) in some cases, so until now this drug is banned in septic patients [11-13].

New investigations claim that less than 10 persons per 100,000 patient-years suffered from lactic acidosis in metformin users with pre-existing illness and organ impairment [14]. In 2012, Green et al. explained that the median level of lactate in metformin group was higher than the control group among septic patients, but all subjects had the same mortality risk [15]. Four years later, in a cohort study Dounias-Barak et al. claimed that mortality rate in septic persons after metformin administration was lesser than the control group [16]. Thereafter, Parker et al. found that the kinetics of lactate did not differ between metformin and non-metformin consumers in septic patients [17]. A substantial role of metformin attributed to AMPK(AMP activated protein kinase) activity. It plays fundamental role in cellular homeostasis via allosteric potential. Also AMPK poses positive effects against inflammation and senescence, which promote synthesis, metabolism and regulation of cellular pathways [18].

AMPK is a heterotrimer kinase with serine/training (Ser/Thr) residues. Phosophorylation of AMPK in Thr172 with metformin leading to AMPK activation. Phosphorylated AMPK is so called p-AMPK. AMPK is known as a natural metabolic switch, when ATP to ADP content falls down, activated cascade reactions leading to inhibition of ATP consumption pathways and stimulate ATP production [19]. Recent experimental studies have shown a close relationship of metformin in AMPK phosphorylation, in sepsis management. In 2013, Park et al. discussed about the role of metformin against bacterial lipo polysaccharide (LPS) infection on in-vivo and ex-vivo models of mice. They concluded that metformin induced p-AMPK, affected bacterial viability via neutrophil chemotaxis facilitation. It has been demonstrated that neutrophil on metformin group invaded bacteria more powerful than the control group and diminished TLR4 [20]. Tzanavari et al. showed that metformin affected AMPK preserved myocardial tissue with the improvement of fatty acid oxidation gene expression level and maintained normal metabolic function of cells in LPS induced sepsis [21]. Next publication claimed that activation of AMPK-α1 after metformin administeration in pulmonary microvascular endothelial cells (PMVECs) culture and murine models relieved alveolar edema, lung tissue permeability improvement and reconstructed micro-circulation of lung tissue after LPS injection [22]. Vaez et al. revealed that metformin pre-treatment influenced cardiomyocyte of septic rats via altered cardiac index, reduced gene expression level of TLR4, MyD88 and TNF-α and elevated rate of p-AMPK. Moreover metformin improved myocardial injury in histopathological assessment [23]. Another publication of Vaez et al. indicated metformin prescription in septic male Wistar rats, leading to upregulation of phosphorylated p-AMPK then after ameliorated lung tissue infiltration and pulmonary congestion, attenuated inflammatory markers such as MyD88, myeloperoxidase (MPO), nuclear factor-κB (NF-κB), Tumor necrosis factor α (TNFα) and doweregulated TLR4 [24]. These two studies represented that metformin may have protective effects on cardiopulmonary damage after LPS induced sepsis on ex vivo models. Liu et al. studied on experimental models of acute lung injury (ALI) after cecal ligation and puncture (CLP) of rats. They confirmed that metformin converted AMPK to p-AMPK improved acute lung injury, restored mitochondrial

complexes (III and IV) function and reduced Hypoxia-inducible factor 1- α (HIF-1α) in macrophages [25] (Figure 1).

In conclusion, a growing body of evidence on in-vitro and in-vivo models revealed that metformin might have a potential role in sepsis management via AMPK activation, modulation of cellular functions and alleviation of multi-organ dysfunction followed by cytokine storms. Moreover, this biguanide drug had a crucial role to protect signaling pathways against oxidative stress and motivating internal cell reactions during sepsis. According to the importance of biguanide administration in septic patients, it should be noted that many differences and questions between experimental cases and human subjects remain unsolved and there is a long way to metformin admnistration in clinical trials . It seems that more research to confirm metformin advantages in septic patients is required. Further laboratory studies will need to focus on larger sample sizes of animals, tracing precise mechanisms of cellular reactions due to sepsis initiation and simulation mammalian models same as the human population will establish more valid and reliable results.

Figure 1- Role of AMPK activation after metformin treatment in experimental models of sepsis.
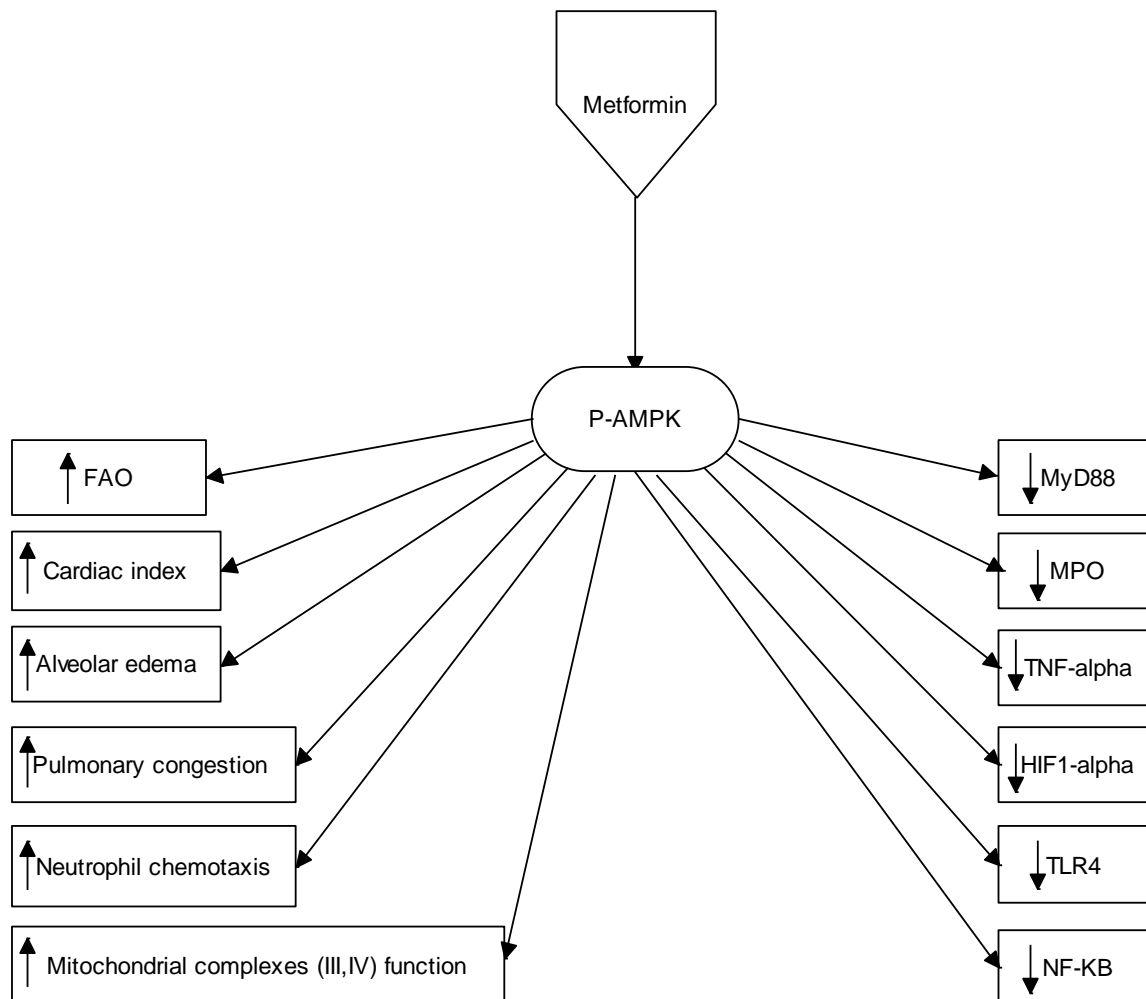
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