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REVIEW ARTICLE

A possible Role of Salicylates in Diabetes Type II

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Abstract

Type II diabetes mellitus is the most characteristic metabolic disorder, described by insulin resistance followed by pancreatic β -cell failure leading to hyperglycemia**.** Inflammation plays a critical role in both insulin resistance and pancreatic β-cell failure. Inflammation induce insulin resistance through stimulation of various serine kinases such as Inhibition of nuclear factor κβ kinase subunit β/ Nuclear factor-kappa Beta (IKK-β / NF-κβ) so, targeting the inflammation with anti-inflammatory agents and preventing insulin resistance may be a promising tool for type II diabetes management. But confirm this approach further researches and evaluation is required. Aspirin (acetyl salicylic acid), for recent use, offers a novel way for management of type II diabetes due to its anti-inflammatory properties and insulin-sensitizing action. Aspirin has the ability to ameliorate hyperglycemia, hyperlipidemia, hyperinsulinemia and insulin resistance and reduce proinflammatory cytokines by several mechanisms. Aspirin has the ability to treat and prevent cardiovascular diseases by inhibition of cyclooxegenase enzyme and act as antidiabetic due to its insulin sensitizing and anti-inflammatory properties. Therefore, aspirin is an effective antidiabetic therapy which is not only providing good glycemic control but also having anti-inflammatory and antithrombotic effects. However, we should keep in mind the side effects that result from its prolonged use which are represented in gastric ulcer, hemorrhage and impairment of kidney function. This review summarizes the responsibility of inflammation in insulin resistance and the role of aspirin as antiplatelets and antidiabetic drug.

Keywords: Aspirin; Type II diabetes; Inflammation; Insulin resistance.

Introduction

Type II diabetes mellitus (T2D) is the most characteristic metabolic disorder, described by insulin resistance followed by pancreatic β-cell failure leading to hyperglycemia [1]. Insulin resistance (IR) is defined as a decreased peripheral tissues response to normal levels of circulating insulin. IR is commonly compensated by hyperinsulinemia. T2D occur when β-cells fail to compensate insulin resistance and lead to insulin deficiency and therefore hyperglycemia and development of complications such as common cardiovascular diseases takes place [2]. Common cardiovascular diseases (stroke, Myocardial infarction) are considered the most critical causes of morbidity and mortality among diabetic patients [1]. Common cardiovascular diseases occur due to athero-thrombosis that include; endothelial cell dysfunction, systemic inflammation that induce vascular damage and prothrombotic and hypofibrinolytic environment [3].

Inflammation plays a decisive role in both IR and pancreatic β-cell failure [3,4]. T2D is considered as inflammatory disorder characterized by increasing circulating levels of cytokines, chemokines and C-reactive protein (CRP) [5]. Nutrients overload such as free fatty acids (FFA), glucose and amino acids through activation of Toll-like receptors (TLRs) lead to increase macrophage infiltration in metabolic tissues (liver, adipose tissue, muscle) and stimulate adipocytes for secretion of chemokines and pro-inflammatory

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cytokines such as Interleukin-6(IL-6), Tumor necrosis factor-alpha (TNF- α), IL-8, IL-1 &IL-1β for inhibition of insulin action and hyperglycemia [6]. Increase of insulin signaling impairment in adipocytes leads to increase lipolysis and increase free fatty acids level in circulation that results in insulin resistance in liver and skeletal muscle [7]. The release of cytokines and chemokines from adipose tissues into the circulation stimulates inflammation in pancreatic islet and other tissues [5].

Inflammation induce IR through stimulation of various serine kinases such as Inhibiton of nuclear factor κβ kinase subunit β/ Nuclear factor-kappa Beta(IKK-β / NF-κβ) by pro-inflammatory molecules, TLRs and receptors for advanced glycation end products (RAGE), elevation of FFA levels, production of reactive oxygen species, endoplasmic reticulum stress and changes in adiposity[6].

NF-κβ is transcriptionally activated by phosphorylation of IKK-β that stimulate proteosomal degradation of inhibitor of NF-κβ (IκBα) allowing the translocation of NF-κβ to the nucleus to binds with specific DNA sequences and increase expression of several target genes(inflammatory molecules) that induce IR as shown in Figure 1. The production of inflammatory mediators further stimulate NF-κβ pathway stimulating vicious loop of IR via feed-forward mechanism [6]. IKK-β stimulates inflammatory response in liver cells that increase the pro-inflammatory cytokines production and then enter the circulation to induce IR in other tissues [8].

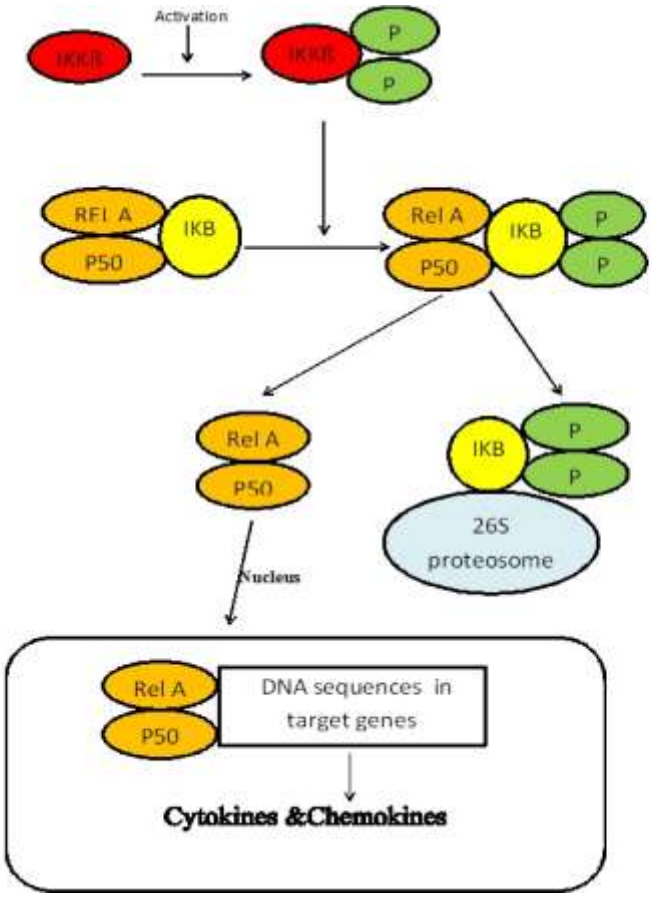

Figure 1: The steps included in the stimulation of the NF-κB pathway (modified) [16]. IKKβ: Inhibitor of nuclear factor κB kinase subunit β, P: phosphorus, IKB: Inhibitor of NF-κβ, Rel A & P50: NF-κB family members

Activation of TLRs stimulates the phosphorylation of insulin receptor substrate-1(IRS-1) (serine residues not tyrosine residues) by c-Jun amino-terminal kinase (JNK) and protein kinase C (PKC) leading to reduction of glucose transporter-4(GLUT-4) [3].

Pro-inflammatory mediators are linked to IR through interfering with insulin signaling pathways. IL-6 is a critical biomarker for the insulin resistance development as it inhibits the non-oxidative glucose metabolism, inhibits the lipoprotein lipase and stimulates the suppressor of cytokine signaling (SOCS) protiens that have adverse effects on the insulin action [8]. TNF- α plays a main role in IR development by activation of IKK-β / NF-κβ and decreasing the expression of GLUT-4 as well as serine phosphorylation of IRS-1[9].

Adiponectin is a unique adipokine which serves as an anti-inflammatory cytokine in a way that can enhance insulin sensitivity [8]. It inhibits expression of TNF- α and IL-6 and hepatic gluoconeogenesis. It stimulates uptake of glucose in skeletal muscles and oxidation of fatty acids in liver and skeletal muscles. On an insulin resistance state, adiponectin are downregulated[10]. Adiponectin has anti-inflammatory, anti-atherosclerotic and cardioprotective effects and acts as an important biomarker for insulin resistance [2].

Based on the data discussed above, targeting inflammation with anti-inflammatory agents and preventing insulin resistance may be a promising tool for management of T2D but these strategies need further researches and evaluation [8].

Aspirin (acetyl salicylic acid) is one of non-steroidal anti-inflammatory drugs (NSADs) that most widely used as an antiplatelet therapy for treatment and prevention of cardiovascular diseases [11]. Aspirin has antidiabetic effect in a dose-dependent manner [12]. Aspirin improves insulin sensitivity and glucose metabolism through questionable unclear mechanism [8, 12].

The increasing prevalence of diabetes makes it imperative that research should focus on its prevention as well as its treatment. An improved understanding of the mechanisms linking inflammation to diabetes and related complications has stimulated interest in targeting inflammatory pathways as part of the strategy to prevent or control diabetes and its complications [4].

This review summarizes the role of inflammation in insulin resistance and the role of aspirin as antiplatelets and antidiabetic drug.

Diabetes Mellitus

Diabetes mellitus is a metabolic disorder which is described by hyperglycemia and/or insulin production or action insufficiency [1].

Types of Diabetes Mellitus according to World Health Organization [13]

Type I diabetes: β-cell destruction (mostly immune-mediated) and absolute insulin deficiency; most common in childhood and early adulthood.

Type II diabetes: most common type, various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity.

Hybrid forms of diabetes:

A) Slowly evolving, immune-mediated diabetes of adults: similar to slowly evolving type1 in adults but more often has features of the metabolic syndrome, a single glutamic acid decarboxylase (GAD) autoantibody and retains greater β-cell function.

B) Ketosis-prone type II diabetes: Presents with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, and not immune-mediated.

*Other specific type*s:

Monogenic diabetes, diseases of the exocrine pancreas, endocrine disorders, drug- or chemical-induced, infection-related diabetes, uncommon specific forms of immune-mediated diabetes, and other genetic syndromes sometimes associated with diabetes.

Unclassified diabetes:

This category should be used to describe diabetes that does not clearly fit into other

categories when there is not a clear diagnostic category especially close to the time of diagnosis.

Hyperglycaemia first detected during pregnancy:

A) Diabetes mellitus in pregnancy: Type I or type II diabetes first diagnosed during pregnancy.

B)Gestational diabetes mellitus: Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy.

Pathophysiology of diabetes

Dietary glucose is the main stimulus for insulin secretion and metabolism of glucose. Also, insulin lowers glucagon secretion and decreases serum fatty acids concentration resulting in decrease of liver glucose production. In fasting conditions, liver provide blood with glucose that is used by the brain in a way may be independent on insulin [1].

Diabetes mellitus complications can be classified into 2 groups:

1) Metabolic acute complications that include hyperglycemia/hypoglycemia episoids, ketoacidosis and hyperosmolar non-ketonic coma.
2) Systemic chronic complications that include microangiopathy, diabetic nephropathy, retinopathy and neuropathy, infections and atherosclerosis [1].

Pathogenesis of Type II diabetes mellitus (NIDDM)

Obesity and several genetic defects are responsible for impairment of insulin secretion from the pancreatic β cells and impairment of insulin action through IR [1].

T2DM is a metabolic disorder described by IR and β-cell failure as a result of prolonged hyperglycemia. In the preclinical period of disease there is a hyperplasia of β-cell and hyperinsulinaemia in response to IR. Then, when β -cells fail to compensate IR, it progress into T2DM with decrease in insulin production [6].

Mechanism of thrombosis and vascular inflammation in diabetes

Atherothrombotic process that leads to vascular occlusion, subsequent myocardial infarction (MI), stroke and complications of diabetes, includes endothelial cell dysfunction (early abnormalities), systemic inflammation (central mechanism induce vascular damage), and prothrombotic and hypofibrinolytic environment [3].

Endothelial cell (EC) dysfunction

The normal endothelium is the key to maintain vascular homeostasis by regulating vasoconstriction and vasodilation, fibrinolysis and thrombosis, platelet activation, leukocyte and platelet interaction, and function of smooth muscle cell. Under physiological conditions, the vascular tone is regulated by the endothelium through production of vasodilator substances such as nitric oxide (NO), and endothelin as vasoconstrictor substances [3,14]. IR with or without hyperglycemia leads to EC dysfunction, resulting in disruption of vascular homeostasis and stimulation of atherosclerosis as the following according to previous literature [3,15]:

1) Expression of adhesion molecules so, attraction of inflammatory cells.
2) Barrier function disruption of these cells resulting in movement of low-density lipoprotein (LDL-c) from vessel lumen to the wall, then it is oxidized to ox-LDL (highly atherogenic).
3) Then, inflammatory cells (macrophages), which moved to the vessel wall from the blood stream, take up ox-LDL due to increase of dysfunctional endothelial cell permeability.
4) This lead to foam cells formation and subsequent fatty streak formation when they aggregate together.
5) After this inflammation, there is a deposition of collagen that leads to beginning of atherosclerotic plaques series.
6) The atherosclerotic plaque ruptures lead to prothrombotic core exposure then platelets activation and vascular clot formation.

Vascular inflammation

Vascular pathology is linked to insulin resistance and hyperglycemia. Decreased NO bioavailability and increased reactive oxygen species (ROS) levels play important role in

diabetes (especially in vascular disease). Insulin resistance leads to vasodilation reduction through inhibition of NO production by decreasing endothelial nitric oxide synthase (eNOS) activity and increasing endothelin-1production [3,16].

Elevation of blood glucose level and FFA levels in diabetes increase ROS production and decreases NO synthesis through several cellular mechanisms. Binding of FFA to Toll-like receptor lead to activation of NF-κβ, that induce inflammation by enhancement the proinflammatory cytokines (IL-6 and TNF-α) expression. Also, the stimulation of TLR activates the phosphorylation of IRS-1 by PKC and JNK resulting in suppression of the phosphatidylinositol 3-kinase/protein kinase B (PI3-kinase/Akt) pathway and GLUT-4. Inhibition of the PI3-kinase/Akt pathway leads to decrease of eNOS activity and NO production [3, 17, 18].

Thrombotic changes

Insulin resistance and hyperglycemia are related to increase activation of platelets and decrease response to antiplatelet drugs [3,19].

Role of chronic inflammation in Insulin Resistance

Role of Insulin Resistance in diabetes

Insulin, the most important regulator of glucose uptake, is a main endocrine hormone excreted by β-cells of pancreatic islets. It`s function is summarized as the following according to Hameed *et al*. [6]:

1- Rapid function: increase glucose transportation and amino acids (A.A) and K+ to insulin sensitive cells.

2-Intermediate function: stimulation of synthesis of protein, activation of glycolysis and glycogen synthesis and inhibition of gluconeogenesis.

3-Delayed function: increase mRNA of lipogenic and other enzymes.

The key feature of T2D is IR that is explained as a state which needs more insulin for the biological actions obtained by a reduced amount of insulin in the normal condition. Obesity, inactivity, and aging are common causes of insulin resistance at the physiological level [20]. Inflammation plays a decisive role in both IR and pancreatic β-cell failure [4, 6].

At normal condition (insulin sensitive state)

Insulin binds to its receptor stimulating signaling cascade resulting in phosphorylation of Tyrosine residue of IRS-1 so downstream insulin signaling [6].

At insulin resistance state

Activation of various serine kinases such as JNK, IKKβ, PKC by pro-inflammatory molecules inhibit insulin action through phosphorylation of serine residue of IRS-1 not tyrosine residue in insulin signaling pathway [6].

IR is related to two prime transcription factor-signaling pathways, NF-κβ and JNK. Activation of these two pathways involves both activators and up regulators of NF-κβ, TLRs and RAGE products, production of ROS, endoplasmic reticulum stress and changes in adiposity. Moreover, elevated FFAs levels causing an increase indiacylglycerol(DAG) that stimulates PKC isoforms resulting in stimulation of NF-κβand JNK pathways[6].

There are different mechanisms involved in inflammation development that induce IR for IKKβ and JNK. JNK phosphorylates the serine residues of insulin receptor substrate -1. Instead, IKKβ stimulates IR by transcriptional activation of NF-κβ [6].

In Brief, diabetes leads to endothelial dysfunction and increasing of pro-inflammatory cytokines, oxidative stress markers and decreasing of antioxidant, anti-inflammatory biomarkers (adiponectin) and presence of macrophage and T-lymphocyte (activated immune cells). These changes can lead to atherosclerosis, accelerated development of arterial thrombosis and increasing risk of death due to common cardiovascular diseases (CVD) [21].

Activation of transcriptional pathways and Insulin resistance

NF-κβ is involved in the insulin resistance pathogenesis. NF-κβ is a transcriptional factor which controls various inflammatory responses. IKK-β is a main activator of NF-

κβ. IKK-β stimulates NF-κβ via phosphorylation and then, NF-κβ stimulates pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β and cause IR. Therefore, IKK-β stimulate inflammation in liver cells that highly increase the pro-inflammatory mediators production which then enter the circulation to induce IR in other tissues [8].

NF-κβ is a transcription factor present in the cytoplasm of each cell and when activated, it is translocated to the nucleus. In resting cells, NF-κβ is associated with one of inhibitory protein molecules known as IκB, including IkBα, IkBβ, IkBε. Inactive NF-κβ / IkB complex is stimulated by phosphorylation via IκB kinases, IKKα and IKKβ leads to polyubiquitination of IkB proteins immediately then rapid degredation of IKB protiens by the 26S proteasome to allow the NF-κβ to translocate to the nucleus for induction of transcription as shown in Figure 1[22].

Activated NF-κβ binds with specific sequences of DNA in target genes, and regulates transcription of inflammatory genes. Thus, IkBα has a critical role on inhibition of NF-κβ, and Ikkβ has a critical role in stimulation of NF-κβ [22].

The production of inflammatory mediators further promotes NF-κβ and JNK pathways inducing a vicious loop of IR via feed-forward mechanism [6].

Role of pro-inflammatory mediators in insulin resistance

Pro-inflammatory mediators play a crucial role in IR and T2DM development via activation of various inflammatory responses [4, 8].

IL-6 and insulin resistance

It inhibits the non-oxidative glucose metabolism, inhibits the lipoprotein lipase that rises the plasma triglycerides levels, stimulates the suppressor of cytokine signaling proteins (SOCS) that may inhibit the cytokine mediated transcriptional factor activation of insulin receptor. SOCS proteins have adverse effects on insulin action and interleukin-6 can stimulate these SOCS proteins. Thus, IL-6 is a critical biomarker for the IR development [8]. Furthermore, IL-6 stimulate leptin and resistin that promote insulin resistance and inhibit adiponectin that is a protective adipokine [10].

TNF-α and insulin resistance

TNF- α is a main pro-inflammatory cytokine that is related to insulin resistance and T2DM development [9].

TNF -α binds to its receptor and activate various transcriptional pathways such as NF-κβ and JNK that lead to phosphorylation of serine 307 in IRS-1 which inhibit insulin action [8]. In addition, TNF-α stimulates resistin and leptin that promotes IR and inhibits adiponectin that is a protective adipokine [10]. TNF- α plays important role in the IR development as it reduces the expression of GLUT4. Activation of TNF- α induce serine phosphorylation of IRS-1, also acts as an inhibitor of insulin receptor and down streams the signaling of PI3K activation. TNF-α inhibit lipoprotein lipase and activate lipolysis in adipose cells lead to increase of non-esterified fatty acids level [9].

Adiponectin as a protective adipokine

FFA and adipokines are the most essential adipose derived mediators. Adipokines involve pro-inflammatory mediators such as TNF-α, leptin, IL-6, tissue inhibitor of metalloproteinases (TIMP-1), adiponectin, retinol-binding protein (RBP-4) and monocyte chemotactic protein (MCP-1). The only adipokine which serves as anti-inflammatory cytokine is adiponectin. It can improve the detrimental effects of MCP-1, IL-6, RBP-4, TNF-α, TIMP-1 and leptin that are originated from adipose tissues [8]. Adiponectin levels decreased in obesity. It is positively related to insulin sensitivity [8]. Adiponectin has the ability for inhibition of tumor necrosis factor-α and IL-6 expression and gluconeogenesis & activation of fatty acid oxidation in skeletal muscle and liver, uptake of glucose in skeletal muscle and insulin secretion [10]. Adiponectin serve as a hormone that can inhibit inflammatory responses *in vitro*. Adiponectin may help in keeping β-cell survival and function, sharing in protection from later development of diabetes. Adiponectin has a protective role in insulin resistance and T2DM [23]. Adiponectin stimulates insulin sensitivity and has anti-inflammatory effects, anti-atherosclerotic effects and cardioprotective

effects. Adiponectin act as a powerful biomarker for IR [2].

Based on the findings in above sections, good glycemic control, optimizing blood pressure control, reducing IR and improving endothelial dysfunction are general measures for reduction the risk of atherothrombosis in diabetes[3]and due to relation between IR and inflammation, targeting of inflammation by anti-inflammatory agents is a good choice for the management of diabetic patients [24]. On the other hand, the studies related to inspection the role of anti-inflammatory drugs for the prevention of insulin resistance are still in their beginning stages and need more basal and clinical studies in the future to improve clinical outcomes [8].

NSAIDs remain the mainstay for treatment and prevention of obesity, T2DM but the efficacy of NSAIDs on lowering the disease progression and prevention of the complications is still far from being applicated and they have adverse effects such as peptic ulcer and renal impairment [12].They were the first class of drugs reported to lower glucose in diabetes more than a century ago. However, several studies with salicylate products have demonstrated an improved metabolic profile in patients with obesity and diabetes, suggesting a potential efficacy for diabetes prevention and control [25-27].

Aspirin, is currently recommended for prevention of CVD, is demonstrated to ameliorate the diabetic disorder and it can converse hyperglycemia, hyperinsulinemia and dyslipidemia due to its insulin sensitizing action [4, 12, 28, 29].

Role of aspirin in T2DM

For treatment and prevention of CVD, aspirin is considered as a cornerstone and most widely used antiplatelet therapy [30]. It is beneficial for secondary prevention of cardiovascular diseases for diabetic patients with a previous history of atherothrombosis. Instead, the aspirin benefit for primary prevention for diabetic patients without a history of atherothrombotic events is unclear [11]. In a dose-dependent manner, aspirin has antidiabetic effect [12].

The American Diabetes Association recommended the use of aspirin (75–162 mg/day) as a secondary prevention in diabetic patients and as a primary prevention in patients with diabetes who have high risk for cardiovascular diseases and after assessment the benefits versus bleeding risk [31].

Aspirin as anti-platelets in diabetes

Diabetes mellitus is considered high risk factor for common cardiovascular diseases (stroke, myocardial infarction). Low dose aspirin (75-100 mg per day) is at least as efficient as high dose but low dose less than 75 mg is of uncertain benefit [11]. Aspirin inhibits COX enzyme by acetylation of hydroxyl group of ser-530 located 70 A.A from C-terminus of COX- 1 and ser-516 of COX- 2 so, inhibits binding of arachidonic acid and subsequent inhibition of prostaglandin synthesis and thromboxane A2 (TXA2) synthesis [32]. Inhibition of TXA2, a potent stimulator of platelet activation, occur for the life time of platelet[11] as platelets don`t have nucleus and can`t regenerates COX so it becomes excellent target for antithrombotic therapy [30]. Aspirin, at lower doses, inhibit COX-1 that responsible for TXA2 but, at high doses, inhibit COX-2 leading to undesirable reduction in prostacyclin (PGI2) production, a vasodilatory and an anti-thrombotic agent. Also, aspirin affect fibrinolysis and fibrin network structure that also give aspirin anti-thrombotic effects [3]. COX enzyme has three isoforms [32]

COX-1 is constitutive form (house keeping), physiologically important as it maintains kidney function, protects stomach mucosa from impairment by HCL and aggregates platelets.

COX-2 is inducible form under pathological conditions, increased by inflammatory mediators and induces inflammation, pain, swelling and fever.

COX-3 expressed from the same COX-1 gene. It is abundant in cerebral cortex and heart. It`s exact role still obscure. It may play roles in mediating pain and fever.

Potential mechanisms of action of aspirin as antidiabetic

Aspirin may act as antidiabetic through inhibition of IKK-β / NF-κβ with inhibition of proinflammatory cytokines especially at high doses [8, 33] and reducing plasma FFA. Salicylates decrease proinflammatory cytokines and increase PPAR-γ and adiponectin so inhibit interaction between adipocytes and proinflammatory mediators [33]. IKK*β* is a key downstream mediator of insulin resistance in T2DM and demonstrated that high doses of salicylates which inhibit IKK*β* activity, reversed hyperglycemia, hyperinsulinemia and dyslipidemia in obese rodents by sensitizing insulin signaling. HBA1c % reduction by higher doses of aspirin in insulin treated rats only supported another mechanism [34].

Furthermore, aspirin was proved to decrease hepatic glucose production and insulin clearance. Finally, aspirin substantial reduce CRP by low or high dose, so an anti-inflammatory mechanism was recommended [28]. Aspirin also may improve glucose tolerance and inhibit prostaglandin E2 (PGE2). There are reports that aspirin increases NO production in cells and tissues and that NO plays an important role in increasing insulin sensitivity. Furthermore, the anti-inflammatory property of aspirin helps in regenerating functional beta cells, glucose stimulated insulin secretion, insulin sensitivity, glucose transport and energy utilization in T2DM [29].

Aspirin might be a peroxisome proliferator and could act by binding to peroxisome proliferator activated receptors (PPARs) and increase the PPAR α / γ mRNA and protein expression in macrophages of liver and kidney of rats [35]. Other studies showed that aspirin binds and activates PPAR γ more than PPAR α [36, 37].The anti-inflammatory effect of NSAIDs may be through activation of PPAR-γ and inhibition of pro-inflammatory gene expression [38].

The antidiabetic effect of aspirin was rediscovered in 1957 when a diabetic patient treated with insulin was provided with a high-dose of aspirin for treatment of arthritis, he no longer needed insulin any more [39].

Antidiabetic effect of high dose aspirin

A systematic review that was carried out on six databases, included 34 randomized control trials (RCTs) and 17 self-control trials, including 13464 participants with T2DM, showed that salicylates ≥3000 mg daily (high dose) ameliorate glucose metabolism, lipidemia and parameters related to inflammation without gastrointestinal bleeding in all studies [40]. Instead, the most frequent adverse effect was tinnitus and it revealed that various doses of salicylates may exert its action through different mechanisms. Thus, salicylates protect patients who has high-risk of CVD by inhibiting COXs enzyme and improve glucose metabolism of diabetic patients by suppression of IKK-β / NF-κβ. This could not prevent patients from receiving low dose aspirin to prevent CVD, but more clinical and basal studies are required before recommending high dose of salicylates for T2D treatment [40].

Treatment of diabetic patients by high-dose aspirin reduces hyperlipidemia, inflammation, and their related cell adhesion [41].

High doses of salicylates (120 mg/kg BW per day) reverse hyperinsulinemia, hyperglycemia and dyslipidemia in obese rodents by inhibition of IKK-β activity and NF-κβ and increase insulin sensitivity *in vitro* and *in vivo* [42].

Treatment of diabetic patients with high doses of aspirin (7 g/day) for 2 weeks, caused reduction in fasting hyperglycemia, triglycerides, total cholesterol, CRP, insulin clearance and gluconeogenesis and improved uptake of glucose by 20% and increase insulin sensitivity [43]. High dose of aspirin has a role in diet-induced IR and in the reversal of obesity [44].

Another study used male albino wistar rats that were received atherogenic diet and treated with aspirin (8 gm⁄ kg) for seven days, declared that there was decrease in the serum LDL-c, glucose, VLDL-c, total cholesterol, and triacylglycerol with increase of HDL-C and insulin[45]. Meanwhile, no notable reduction in fasting glucose level, significant decrease of hepatic NF-κβ expression and serum TNF-α level and insulin resistance improvement were reported in diabetic male

wistar rats that were received aspirin (120 mg/kg BW/day) for 8 weeks [46].

Antidiabetic effect of low dose aspirin

There are some experimental studies that revealed that low dose aspirin has the ability for improving diabetic process with no more benefit from using high doses [28, 29] and this need further clinical studies to being applicated. Obese wister albino rats that were treated with low dose aspirin (25mg/kg) for seven days showed significantly decreased fasting blood sugar, triacylglycerol, cholesterol, fasting blood sugar (FBS) and body weight (BW)[47]. Goto-Kakizaki (GK) diabetic rats with low dose aspirin 100 mg/kg BW for 5 weeks showed significant improvement in glucose tolerance accompanied by significant decrease in insulinemia, pro-inflammatory prostaglandin, PGE2, the total cholesterol and lipoprotein levels [29]. Also, Lou *et al*. [48] reported that low dose of aspirin had a beneficial effect in reducing serum low density lipoprotein, Lp (a) and Hs-CRP levels and improve coronary heart disease with slightly increase gastrointestinal bleeding risk. Lin and his coworkers [49] treated Sprague-Dawley (SD) rats with high fat diet for a 10-week with low dose of aspirin (5 mg/kg Bw) found that low-dose aspirin ameliorated hyperinsulinemia and hyperlipidemia, recovered activated partial thromboplastin and prothrombin time, prevent adhesion molecules expression and chemokine formation. Rat pups (neonates) that were treated with 10 mg/kg BW aspirin for one month after streptozotocin administration showed significant reduction in blood glucose levels and insulin resistance and significant improvement in insulin levels and insulin sensitivity [50].

Moderate and high dose aspirin have better effect on fasting blood glucose levels of diabetic male albino rats, but high triacylglycerol level was reports in comparison with the diabetic non treated rats [34]. In contrast, contradictory results were obtained by Abdin and his coworkers [28] that the diabetic male albino rats which were treated with 10 mg/kg BW and 120mg/kg BW aspirin showed no significant reduction in levels of insulin with notable reduction of insulin resistance, levels of TNF-α ,IL-6, FFAs and fasting glucose. They recommended the use of low-dose aspirin as an effective and safe drug for diabetes with no more benefit from using high doses due to its adverse effects.

Aspirin induces glucagon and insulin secretion and increases glucose tolerance in diabetic and normal subjects[51], while acetyl salicylic acid decrease glucose intolerance in maturity onset diabetics by a direct stimulation of insulin secretion[52].

In contrast, early studies showed that salicylates increase insulin resistance in diabetic patients although decrease of fasting blood glucose (may be due to increase plasma response to insulin) [53] and normal patient [54, 55]. This difference in the effect of salicylates may due to the difference in the experimental model and the studied species [34].

Aspirin side effects

Aspirin prevents thrombosis by inhibition of prostaglandin synthesis, that leads to negative side effects, including toxicity of upper-gastrointestinal (GI), intracranial and extracranial haemorrhage due to the inhibition of COX-1 and subsequent PGE2 synthesis by aspirin. While PGE2 increases mucous formation and inhibits secretion of acid in gastric mucosa. Therefore, buffered and enteric coated aspirin were developed to minimize this side effect [56].

Also, chronic high dose of aspirin may lower renal blood flow and glomerular filtration and cause damage of kidney function due to the inhibition of COX-2, subsequent inhibition of PGI2 which diminish vascular resistance and support renal perfusion [57].

Furthermore, high-dose aspirin may reduce the benefit of angiotensin-converting enzyme (ACE) inhibitors in hypertensive and congestive heart failure patients due to inhibition of PG E3 and PGI2 synthesis, which is stimulated by ACE inhibitors [30].

In Brief, some studies on experimental rat models of diabetes and clinical trials have revealed the beneficial and detrimental effects of aspirin on complications associated with diabetes and insulin sensitivity depending on

the aspirin doses and experimental models used[29,40,47-49].

Conclusion

Diabetes management should not only target the glycemic control but also should focus on the mechanism to improve insulin resistance. Aspirin, for recent use, offer a novel way for management of type 2 diabetes due to its anti-inflammatory properties and insulin-sensitizing action. Aspirin is an effective antidiabetic therapy which is not only providing good glycemic control but also it has anti-inflammatory and antithrombotic effects. Meanwhile, we should keep in mind the side effects that result from its prolonged use which are represented in gastric ulcer, hemorrhage and impairment of kidney functions.

Conflict of interest

The authors have no conflict of interest to declare.

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الملخص العربي

دورالسالسيلات في علاج داء السكري من النوع الثاني

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مرض السكري من النوع الثانى هو أكثر اضطرابات التمثيل الغذائي شيوعا ، التي تتميز بمقاومة الأنسولين تليها فشل الخلية بيتا البنكرياسية مما يؤدي إلى فرط سكر الدم. يلعب الالتهاب دور هام في كل من مقاومة الانسولين و فشل خلايا بيتا البنكرياسية. الالتهاب يحفز مقاومة الإنسولين من خلال تفعيل serine kinasesمختلفة مثل (IKK-β /NF-κβ) مانع العامل النووي kappa بيتا \ العامل النووي kappa بيتا .لذلك ، استهداف الالتهاب بواسطة مضادات الالتهاب ومنع مقاومة الانسولين يمثل أداة واعدة للتحكم في داء سكّريّ من النوع الثانى ، غير أنّ هذه الإستراتيجيات تحتاج العديد من الابحاث والتقييم فيما بعد .يعد الأسبرين، عقار قديم للاستخدام الجديد، لكنه يقدم أساليب فريدة لعلاج مرض السكري من النوع الثانى بسبب قدرته علي زيادة حساسية الخلاياللأنسولين وكذلك خصائصه المضادة للالتهابات .بالاضافة الي ان الأسبرين لديه القدرة على تخفيف فرط سكر الدم، فرط الدهون في الدم، فرط الانسولين في الدم وايضا تخفيف مقاومة الأنسولين وتقليل السيتوكينات السابقة للالتهاب من خلال عدة آليات.الأسبرين لديه القدرةعلى العلاج والوقايةمن أمراضالقلب والأوعيةالدموية عن طريق تثبيط إنزيمcyclooxegenase و يعتبركمضادالسكري بسبب قدرته علي زيادة حساسيةالأنسولين وامتلاكه خصائص مضادة للالتهابات،كما يعتبرالأسبرين العلاج الفعال ضدالسكري الذي لايوفرالسيطرةالجيدةعلى مستوى السكرفي الدم فحسب ولكن أيضاله آثارمضادةللالتهابات ومضادةللتخثر. ولكن يجب ان يؤخذ في الاعتبار الآثار الجانبية التي تنجم عن استخدامه لفترات طويلة والتي تتمثل في قرحة المعدة، والنزيف، وتعطيل وظائف الكلى. يلخص هذا المقال دور الالتهاب في مقاومة الأنسولين ودور الأسبرين كمضادات للصفيحات والعقاقير المضادة للسكري.