مجلة المثنى للعلوم الصرفة
AL-Muthanna Journal of Pure Sciences (MJPS)
VOL.(3)...NO.(1) ….2016

The effect of high – dose of Aspirin in Improve glucose metabolism and its role in triglyceride and C-reactive protein, in type 2 diabetes

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Abstract

The researches and experiment has been continued since 1901 about using aspirin in treatment ,Aspirin is a weak organic acid that is unique among the NSAIDs in that it irreversibly acetylates (and, thus, inactivates) cyclooxygenase (COX) is responsible for the in sites of disease and inflammation. My research have implicated fatty acid-dependent activation of the serine kinase IKKβ (aspirin could specifically inhibit the protein I-kappa-β-kinase beta is essential for inflammatory cytokine-induced activation of nuclear factor (NF-κB) in the pathogenesis of insulin resistance. To test this hypothesis, we studied ten type 2 diabetic subjects before and after(10-14 days)of treatment with aspirin plays a pivotal role in the function of major cell types that contribute to the pathophysiological process for inflammatory , which plays a key role in tissue inflammation, in the pathogenesis of insulin resistance. High doses >1g/day of salicylates have recently been shown to inhibit IKKβ activity and might therefore ameliorate insulin resistance and improve glucose tolerance in patients with type 2 diabetes. To test this hypothesis, we studied Ten type 2 diabetic subjects before and after (10 -14 days) of treatment with aspirin (>1 g/d). Subjects underwent mixed-glucose turnover before and after treatment. High-dose aspirin treatment resulted in a ~20 % reduction in fasting plasma glucose, associated with a ~15% reduction in total cholesterol and C-reactive protein, a~40% reduction in triglycerides, and a ~30% reduction in insulin clearance, despite no change in body weight During a mixed-meal tolerance test, the areas under the curve for plasma glucose and fatty acid levels decreased by ~20% and ~40%, respectively. Aspirin treatment also resulted in a ~20% reduction in basal rates of hepatic glucose production and a~20% improvement in insulin-stimulated peripheral glucose uptake under matched plasma insulin concentrations during the clamp. In conclusion, these data support the hypothesis that IKKβ represents a new target for treating type 2 diabetes mellitus.

Aim of study

Use Aspirin in protocol treatment diabetic type /2 help patients in different dose (high dose) aspirin treatment improved both fasting and postprandial hyperglycemia in patients with type 2 diabetes, an effect that could be attributed to decreased basal rates of hepatic glucose production, enhanced peripheral insulin sensitivity, and decreased insulin clearance and reduction in total triglyceride and C-reactive protein.

Introduction

Aspirin salicylic acid is the prototype of traditional NSAIDs (Nonsteroidal Anti-inflammatory Drugs). It is the most commonly used and is the drug to which all other anti-inflammatory, antipyretic, analgesic, agents are compared, mechanism of action all of the act by inhibiting the synthesis of prostaglandins, inhibits cyclooxygenase (COX1 & COX2), activity, reduces the level of platelet TXA2 [1-2]. Mystudies Insulin resistance is a primary factor in the development of type 2 diabetes. Recent studies have implicated fatty acid activation of a serine/threonine kinase cascade in the pathogenesis of insulin resistance. Recently hypothesized that IKKβ is a key downstream mediator in this process and demonstrated that high doses of salicylates, which inhibit IKKβ activity, reversed hyperglycemia, hyperinsulinemia, and dyslipidemia in obese rodents by sensitizing insulin signaling. Evidence that these effects were mediated by salicylate inhibition of IKKβ activity, as opposed to inhibition of cyclooxygenases, was obtained by demonstrating that heterozygous deletion of IKKβ protected mice against the development of insulin resistance during high-fat feeding or lipid infusion. However [3-10] the effects of aspirin in patients with type 2 diabetes are less clear. While early studies suggested a salutary effect of aspirin on glucose metabolism in diabetic patients, more recent clinical trials have demonstrated a detrimental effect of aspirin therapy on insulin sensitivity. There are Important differences between these studies included lower aspirin dosages (<1 g/d) and therapeutic duration (a few days) in the more recent studies than in the earlier studies (>1 g/d for 10-14 days), we decided to examine this hypothesis in patients with type 2 diabetes. We measured basal and insulin-stimulated rates of whole-body glucose metabolism before and after high-dose aspirin therapy (>1g/d) using hyperinsulinemic-euglycemic clamps. In addition, mixed-meal tolerance testing was done before, during, and after the aspirin treatment [11-12].

Materials and Methods

Ten subjects with type 2 diabetes (five men and five women, age between (45-75) year weight between 55-108 kg, body surface area 2.2± 0.1 m2, body mass index 35±3 kg/m2) were studied before and after (10-14) days of treatment with aspirin [13-15]. All the patients were initially screened to rule out any other systemic disease and any biochemical evidence of abnormal renal or hepatic functions. Patients with a history of alcohol abuse, symptomatic coronary heart disease, stroke, current use of insulin for glycemic control, significant hepatic enzyme elevation (more than twice the upper limit of normal), serum creatinine greater than 1.5 mg/dl, history of ketoacidosis or current metabolic acidosis, history of gastric ulcer, dyspepsia, upper or lower gastrointestinal bleed, history of allergy to aspirin, or bleeding diathesis, or currently on oral anticoagulants [16-17] were excluded from the study. Women who were pregnant, lactating, or of childbearing potential and not using a barrier or hormonal method of contraception were also excluded from the study.

The subjects were asked to stop their antidiabetic medications 3-day before the

study period. Two subjects were diet-controlled and taking no anti-diabetic medications, whereas others were on either a sulfonylurea and/or metformin. Given the relatively short biological half-lives of sulfonylurea and metformin compared with thiazolidinediones, it is likely that there were no residual effects of these compounds on any of the base-line parameters. Furthermore any residual effects of these agents would lead to an underestimation of the effect of high-dose aspirin on glucose metabolism. For 3 days prior to each patient study, the subjects were given a diet containing 35 kcal/kg body weight, consisting of 60% carbohydrate, 20% fat, and 20% protein, prepared by the hospital or house kitchen, and asked to abstain from alcohol, caffeine, and exercise, except for normal daily activities. The same diet was continued during their stay in theexperiment. The protocol was reviewed and approved by the laboratory Investigation Committee. Informed written consent was obtained from each subject [18,26].

Study design

Subjects were screened at the outpatient facilities of the (GCC-diabetic), including physical examination, urine analysis, and a check of routine chemistries, fasting lipid panel, cell blood count, prothrombin time/partial thromboplastin time, (INR), serum glutamic oxaloacetic transaminase, alkaline phosphatase, and β human chorionic gonadotrophin for females. Stools were checked for blood by hemoccult cards. the washout period, each subject was admitted to the (GCC-diabetic), each subject was started on 20mg omprazol Two-Three times per day, to prevent aspirin-induced gastric ulcers, 3 days before the first patient visit (5 days before the first base-line clamp study), and the omprazol was continued for the duration of the study. After their admission laboratory, subjects underwent a 24-hour urine collection for assessing urine creatinine and nitrogen excretion. [4,5,6,7,8,19].

Treatment period

Upon completion of the base-line study, subjects were started on enteric-coated aspirin (>1 g/d) divided in three equal doses (every 8-hoers–dose 250- 350 mg) for 10-14 days. Blood salicylate and electrolyte concentrations were monitored every 1–2 days, and one week after the initiation of aspirin, patients were readmitted for mixed-meal tolerance testing. In addition, the subjects were seen as outpatients every other day during the treatment period to measure safety parameters (adverse event query, vital signs, stool guaiac) and to monitor compliance by blood salicylate level. At the end of 10–14 days of study, subjects were readmitted to (GCC-diabetic) and underwent the same procedures as during the base-line period, with a mixed-meal tolerance test on the first day and then hyperinsulinemic-euglycemic clamp on the second day. At the completion of the study, the subjects were instructed to restart their antidiabeticmedications [19-22] .

Mixed-meal tolerance test.

Aspirin treatment resulted in a significant decrease in plasma glucose concentrations during the mixed-meal tolerance tests (21% decrease in area

under the curve [AUC], P =0.0001); this decrease was associated with a 34% increase (AUC, P=0.0003) in plasma insulin levels, but no difference in C-peptide levels (AUC, P=0.31) .There was no difference in fasting plasma concentrations of insulin, C-peptide, or glucagon (data not shown). Aspirin treatment also caused an approximately 50% decrease in fasting plasma fatty acid concentration (727±76 vs. 379±43 μM) and a 52% decrease (P=0.005) in AUC for the plasma fatty acids levels [23–26].

Conclusion

High dose Aspirin treatment improved both fasting and postprandial hyperglycemia in patients with type 2 diabetes, an effect that could be attributed to decreased basal rates of hepatic glucose production, enhanced peripheral insulin sensitivity, and decreased insulin clearance. In view of the potential toxicities associated with chronic high-dose aspirin, we would strongly advocate against its use for treatment of type 2 diabetes. However, these data are consistent with the hypothesis that a serine kinase cascade is involved in the pathogenesis of insulin resistance in type 2 diabetes and suggest that the IKKβ pathway may represent a new target for treating this disease.

Results

Base-line characteristics of diabetic subjects, before and after(10-14days) of treatment with aspirin, (Table 1) and average dose of aspirin was >1 g, with a mean plasma salicylate level of 27.4± 2.0 mg/dl. There was no significant change in body weight. All the patients completed the study with no major side effects. The only minor side effects were tinnitus and short time hearing loss, which tended to decrease with continuation of the treatment and disappeared completely after the aspirin was stopped. A few subjects had transient diarrhea, flatulence, and abdominal cramps at the start of omprazol, which disappeared as they continued the medication. Although the mean plasma bicarbonate concentrations decreased by 4 mM following aspirin therapy, this was not felt to be clinically significant since the concentrations were still in the normal range and were unassociated with an anion gap. Liver enzymes did not change during the aspirin therapy. Two weeks of aspirin treatment resulted in a drop of about 40 mg/dl in fasting plasma glucose concentration, and this drop was not associated with any episodes of hypoglycemia. There was a small but significant decrease in creatinine clearance rate (12%) that normalized following discontinuation of aspirin. There were also significant decreases in concentrations of plasma cholesterol (15%), HDL cholesterol (10%), triglycerides (40%), and C-reactive protein (15%).

Discussion

Glucose tolerance was improved by aspirin therapy in diabetic subjects [B13, B15], and aspirin was shown to reduce insulin requirements [B14]. Conflicting results on the effects of aspirin in normal and diabetic subjects were subsequently reported. In view of the recent rodent data demonstrating a potentially important role of IKKβ in mediating insulin resistance in obesity and the ability of high-dose salicylate to inhibit IKKβ activity, we decided to examine whether high-dose aspirin would ameliorate insulin resistance

in patients with type 2 diabetes. We found that a 2-week trial of high-dose aspirin treatment was accompanied by significant decreases in hepatic glucose production (22%), fasting plasma glucose (24%), fatty acids (50%), and triglycerides (48%) and a 19% increase in peripheral glucose disposal. The reductions in fasting plasma glucose concentration and glucose production are comparable to the effects of metformin in type 2 diabetic patients and occurred independently of any changes in fasting plasma insulin or C-peptide concentrations. In contrast, the aspirin-induced increase in insulin-stimulated glucose uptake observed during the clamp study was associated with an approximately 47% increase in plasma insulin concentrations, which could be attributed to decreased insulin clearance. After matching these higher insulin levels during a repeat hyperinsulinemic-euglycemic clamp study, peripheral glucose uptake rates were still about 25% higher, demonstrating that high-dose aspirin improves peripheral insulin sensitivity. These data are consistent with recent animal studies demonstrating that high-dose aspirin therapy protects against fat-induced insulin resistance through inhibition of IKKβ activity.

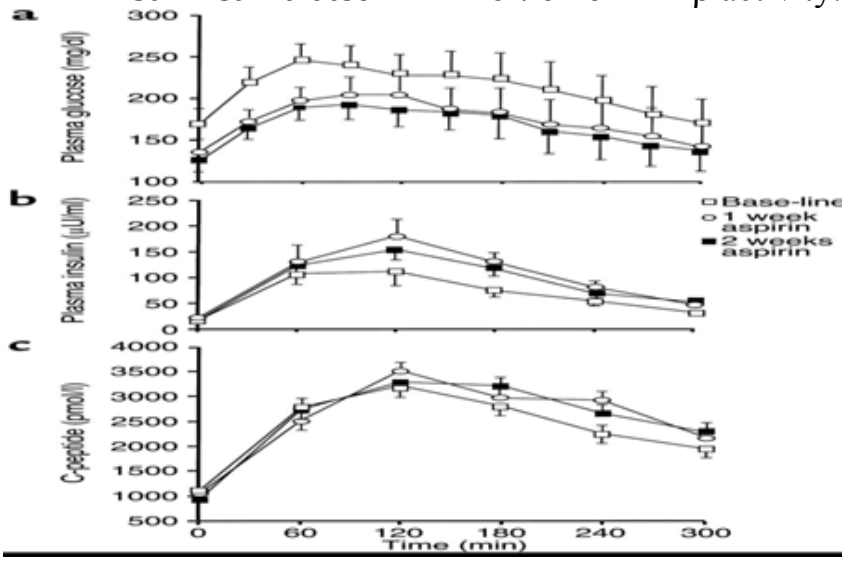

Figure : 1 AUC (Area under the curve)

Mean plasma concentrations of glucose (a), insulin (b), and C-peptide (c) during mixed-meal tolerance testing.

Table1: Patient characteristics before after Aspirin treatment :

Base-line		After tretmant
1) Weight (Kg)	82 kg ± 5.0	83.6 ± 5.5
2) Body surface area (m2)	2.2 ± 0.1	2.2 ± 0.1
3) Fasting plasma glucose (mg / dl)	170 ± 20	130 ± 15
4) Creatinine clearance rat (ml / min)	140 ± 8	123 ± 8
5) Serum sodium (mmol/ L) 138 ± 0.7	140 ± 0.8	
6) Serum chloride (mmol / L)	102 ± 0.6	109 ± 1.1
7) Serum bicarbonate (mmol / L)	25 ± 0.8	21 ± 1.0
8) Triglyceride (mg /dl)	227 ± 20	213 ± 10
9) C-reactive protein(mg /dl)0.71 ± 0.40	0.39 ± 0.4	

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الخلاصة:

أن الأبحاث والتجارب مستمرة منذ عام 1901 حتى يومنا هذا حول استخدام الأسبرين Salicylic acid هو مركب فريد عضوي ضعيف حامضي ضمن مجموعة المضادات الالتهابات الغير الستيرويديه (NSAIDs) يثبط عمل أنزيم cyclooxygenase (COX) المسؤول ويتحرر في منطقة الإصابة ويعمل التهابات في بحثنا عملنا (تركيز) على نوع من الشحوم الحامضية يعمل على تفعيل بروتين I-Kappa-B–(Kinase beta (أنزيم IKKB الذي يعمل الاسبرين بصورة خاصة على هذا البروتين (أنزيم) المسؤول الاساس في الالتهابات ومقاومة الجسم للأنسولين Insulin resistance) فعملنا الدراسة والبحث على عشرة أشخاص (5 ذكور و5 أناث) في المركز السكري للمرضى النوع الثاني type 2) من داء السكري قبل أعطاء الجرعة وبعد أعطاء الجرعة للفترة (10–14 يوم) من العلاج بالأسبرين وجدناه فعال وله أهمية في الوظيفة الخلايا من ناحية المرضية والوظيفية بتثبيط هذا البروتين (الانزيم) ويعتبر المفتاح للالتهابات الأنسجة ويعمل على زيادة مقاومة الجسم للأنسولين، قمنا بأعطاء جرعة عالية من الاسبرين اكثر من 1غم باليوم مع أخذ الاحتياطات اللازمة أعطاء omprazol 40 mg or mesoprascetol وجدنا تثبيط لهذا البروتين أنزيم) (IKKB يحسن ويقلل من مقاومة الجسم للأنسوليين ويقلل من الحمل على مقاومة للأنسولين لذلك يشعر المريض بتحول قبل أعطاء الاسبرين وبعد أعطاء الاسبرين وعند القياس كل صباح المريض صائم 20% يقل السكر في بلازما الدم مع 15% الكولستيرول total cholesterol) و(C-reactive protein) و(40 % يقل الشحوم الثلاثية (triglycerides) و30% يقل (insulin clearance) بالرغم لا يوجد تغيير في وزن المريض (body weight)،وخلال تناول الطعام منوع 20% يقل (in basal rates of hepatic glucose production) و20% يقل من مقاومة للأنسلين ويحسن من أفرازه في الانسجة المحيطية، وهذا يمثل أنطلاق جديدة في علاج داء السكري النوع الثاني type2.