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Montelukast influence on kidney in experimental induced diabetes mellitus

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Abstract: Leukotrienes are important icosanoids group involved in a lot of normal and pathological states. Montelukast (MK) is a selective cysteinyl leukotriene receptor (Cys LT1) antagonist. Purpose. The purpose of the study is to observe the influence of MK on renal damage caused by experimental diabetes in rats. The experiment was carried out on four groups of adult male Wistar rats. Lot I was a witness and received 1.5ml of physiological saline ip. in unique dose on the first day of the experiment. Lots II and III have been caused experimental diabetes by streptozotocin (STZ) administration of 60mg/kg ip. in the unique dose. Lot III also received MK daily 10mg/kg/day daily 8weeks.Lot IV received only MK 10mg/kg/day daily 8 weeks. After eight weeks all animals were anesthetized and were sacrificed. The following pathological modifications were observed: tubular injury, glomerular hypertrophy and lesions, leukocytes infiltration. Obtained data showed that MK has significantly reduced the intensity of glomerular lesions (score 3.50+/-0.21 in STZ lot vs. 2.50+/-0.17 in STZ+MK lot $p<0.01$) and tubular damages. Renal interstitial leukocyte infiltration in animals with diabetes has been also reduced by MK. MK has a partially protective action against the lesions produced by experimental diabetes.

Keywords: kidney, montelukast, diabetes, glomerular lesions, tubular damages.

INTRODUCTION

Diabetes mellitus has become a serious public health problem worldwide.According to WHO estimates were worldwide 422 millions diabetes patients in 2016. The number of people with diabetes worldwide has doubled during the past 20 years and is constantly growing (Zimmet *et al*.2014, Zheng *et al*., 2018) There are predictions that the number of people with diabetes will increase worldwide by 2040 to about 642 million (Ogurtsova *et al*., 2017) There are many complications of diabetes: heart disease, diabetic retinopathy, dyslipidemia, the development of atheromatosis, neurological and psychiatric complications and others (Forbes and Cooper 2013). The kidneys are some of the most affected organs in diabetic patients. Renal damage is one of the most important complications of diabetes.

Leukotrienes are a very important icosanoids group involved in a lot of normal but also pathological states in human body (Haeggström and Funk 2011, Kanaoka and Austen 2019). This group of biologically active lipids is synthesized from arachidonic acid. This polyunsaturated fatty acid is released from membrane phospholipids under the action of phospholipase A2 and phospholipase C. The main enzyme in the synthesis of leukotrienes is 5-lipoxygenase (5 -LO). This enzyme activity requires the presence of 5-LO activating protein (FLAP). Under its action arachidonic acid is transformed into leukotriene A4 (LTA4) from which two groups of leukotrienes are generated: leukotriene B4 and cysteinylleukotrienes (LTC4, LTD4 and LTE4). LTB4 is generated from LTA4 by epoxide hydrolase action. This hydrolase is located in all segments of the nephron.

LTC4 is synthetized from LTA4 under the action of glutathione S-transferase. LTD4 is formed from LTC4 under the action of γ-glutamyl transferase and LTE4 is produced by transforming LCD4 under the action of a dipeptidase. Genes corresponding to 5-LO synthesis have been identified have in many rat or human nephron structures, but it does not exist in glomerular epithelial cells or in renal mesangial cells. At all parts of the nephron there are cys LT1 receptors (Reinhold *et al*., 2006). 5-LO was not identified in glomerular epithelial cells or in renal mesangial cells but is abundant in polymorpho nuclear cells and other kidney cells.

Due to this, the synthesis of LTB4 and peptidoleukotrienes has a trans cellular character (Wang *et al*., 2019). LTA4 synthesized into neutrophils and macrophages is transformed into LTC4 by the action glutathione S-transferase that exists at the glomerular, tubular and mesangial level (Katoh *et al*., 1993, Yan *et al*., 2019). LTA4 produced in leukocytes under the action of 5-LO is transformed into other leukotrienes at the level of the entire nephron in both the glomerular and tubular levels (Reinhold *et al*., 2006, Shioda *et al*. 2023). Macrophages and neutrophils in renal infiltrates are also an important source of leukotrienes that act in the kidneys. Renal synthesis of cysteinyl leukotrienes has also

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been shown by experimentally monitoring of urinary excretion of LTE4.

For peptidoleukotrienes there are different receptors than receptors for LTB4 (Kanaoka and Austen 2019). LTC4, LTD4 and LTE4 act on cysLT1 and cysLT2 receptors. These are membrane receptors with a wide distribution in the human body. Cys LT1 receptors are located at the glomerular level, in all parts of the nephron but also at the level of mesangial cells. Cys LT2 receptors are not found at the glomerular and tubular level. Leukotrienes are involved in glomerular and tubular lesions.

Montelukast (MK) is a selective cysteinyl leukotriene receptor (cys LT1) antagonist. MK is considered for use as first-line therapy in patients with bronchial asthma (Trinh *et al*., 2019) in adult and in children but this drug is used also in the treatment of asthmatiform bronchitis, allergic rhinitis and bronchiolitis obliterans syndrome (Jarvis and Markham 2000, Ruttens *et al*., 2018). Leukotrienes synthesis is increased in diabetes mellitus and it is involved in the development of some diabetic complications (Talahalli *et al*., 2010 Ramalho *et al*., 2018).

The aim of this study is MK influence on kidney diabetic lesions in experimental induced diabetes mellitus.

MATERIALS AND METHODS

Worked on four groups of 8 adult Wistar rats, males weighing 240-260g grown under normal laboratory conditions and in boxes polycarbonate and identically fed.

Animals were obtained from Laboratory Animal Center of Cantacuzino Institute of Research, Bucharest, Romania and were housed in groups of four in Plexiglas cages (65x40x30cm). The experiment was carried out on adult male Wistar rats (body weight 220-250g). Animal were housed in polycarbonate cages (4 animals per cage). During the experiment the animals were kept at a temperature of 22-24ºC, in a constant 12-hour light/12-hour dark cycle, with free access to water and standard food.

Group I was a witness and received 1.5ml of physiological saline ip/kg. in unique dose on the first day of the experiment. Lots II and III have been caused experimental diabetes by streptozotocin (STZ) (Sigma Aldrich St Louis USA) administration of 60mg/kg ip. in the unique dose (Molehin and Oloyede 2010). Group III also received daily 10mg/kg montelukast (MK) (Actavis Malta) by endogastric probe.Group IV received only montelukast 10mg/kg/day daily 8 weeks. The weight of the animals was determined every two days. Doses were adapted to animals weight variations during the experiment.

Initial (prior to administration of any substance), 72h after STZ administration and at the end of the study, blood sampling was performed from all animals and plasma glucose concentration was determined. Blood glucose was measured after an overnight fast.

Blood samples from the tail were taken from each animal and were centrifuged at 6500 10 minutes. Serum glucose levels were measured by spectrophotometric method using Randox Daytona UK analyzer. Kits and reagents used were produced by Randox Laboratories LTD, UK. Rats were considered diabetic when blood glucose levels reached>220mg/dL a 72h after STZ administration.

Increased lipid peroxidation is one of the most important pathogenic mechanisms of damages production in diabetes mellitus. Malondialdehyde (MDA) is an important secondary product resulting from lipid per oxidation. Measurements of MDA levels, as a biomarker of oxidative stress. The level of the lipid per oxidation product MDA was determined spectrophotometrically. MDA was tested using a thiobarbituric acid (TBA) assay. MDA reacts with TBA and generates a colored with maximally absorbtion at 535nm (Buege and Aust 1978). After eight weeks all animals were anesthetized with thiopental 40mg/kg ip. and were sacrificed by carotid sectioning.

The kidneys were removed from all animals. Both kidneys of all animals were weighed after slaughter and after that both kidneys of each animal were examined in optical microscopy using an Optika microscope (Optika Italy 2004). The harvested kidneys were fixed in buffered neutral solution of formalin 10% and all were processed histopathologically by usual method.

Seven section 5 microns each from both organs from each animal were performed with a Microtome SLEE CUT 6062 (SLEE Medical GmbH, Germany). Sections fixed in paraffin were stained using Hematoxylin -Eosin, PAS and Tricromic Szekelly method. Ten images per section were examined. The following pathological modifications were observed: tubular injury, glomerular lesions, interstitial infiltration. The observation of histopathological lesions was made by two independent observers. The following histopathologically glomerular lesions were followed: focal glomerulosclerosis, glomerular hypertrophy, glomerulosclerosis, mesangial expansion, enlargement of the glomeruli. At least two hundred glomeruli per animal were scored.

The following lesion score (Canales *et al*., 2012) was used to assess the intensity of the glomerular lesions: 0=intact glomeruli; 1=glomerular lesions affecting less than 10% of the total area studied; 2=glomerular lesions affecting 11%-25% of the total area studied; 3=lesions glomerular affecting 26- to 50% of the total area studied;

4=lesions glomerular affecting more than 50% of the total area studied.

Tubulointerstitial damages was defined as tubular necrosis, intratubular casts, tubular lumen dilation or tubular atrophy. The tubular damage was scored on a scale of 0 to 4:0 = normal; 1=involvement of less than 10% of the renal tubules studied; 2=involvement of 10-25% of the renal tubules studied; 3=involvement of 26-75% of the renal tubules studied; 4=extensive damage involving more than 75% of the renal tubules studied (Shih *et al*., 1988, Francescato *et al*., 2012).

The interstitial space has been defined as the space that is not occupied by the glomeruli, blood vessels or renal tube.

For each animal, 30 areas were photographed using a 40x objective lens and the interstitial area was evaluated. Leukocyte interstitial infiltration was scored on a scale from 0 to 2: 0=absence of infiltration; 1=infiltration only in relation to interstitial fibrosis and tubular atrophy (IFTA); 2=infiltration in areas without IFTA (Tervaert *et al*., 2010).

STATISTICAL ANALYSIS

Obtained data were statistically interpreted by one way ANOVA test implemented in the SPSS Analytics variant 17.0 software for Windows. Data are given as mean±SD. A value of P<0.05 was considered significant. The research was conducted after obtaining the agreement of the Ethics Committee of Research of "Gr. T Popa" University of Medicine and Pharmacy and was in agreement with the EU directive 2010/63/EU regarding to the handling of laboratory animals.

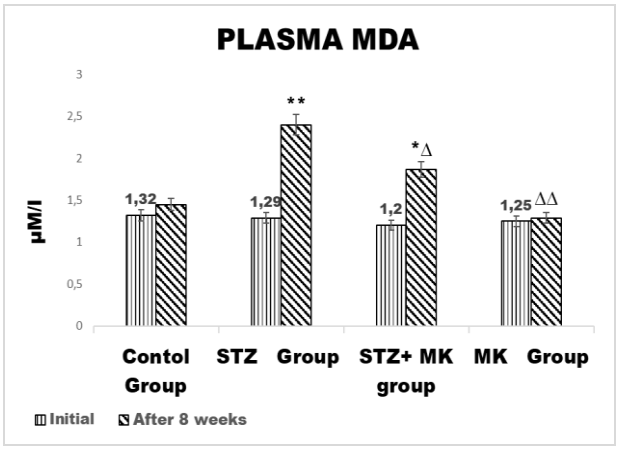
RESULTS

Fasting plasma glucose level was significantly increased by STZ administration. After 72h plasma glucose level was higher to 220mg/dl in all animals treated by STZ. Administration of MK to animals receiving STZ did not significantly alter plasma glucose levels compared to animals receiving STZ alone.

Fasting blood glucose was not altered in rats treated with MK only when compared to control rats (table 1)

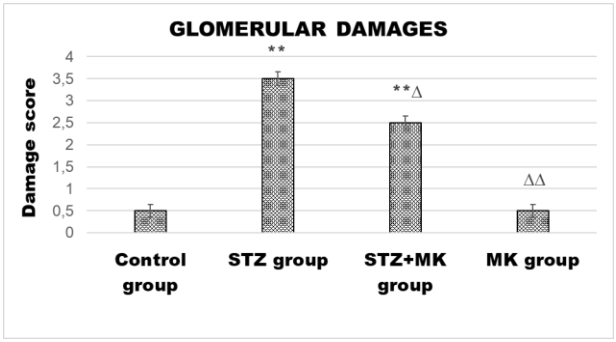
STZ administration increased MDA level the association of MK with STZ decreased the MDA level compared to the group that received only STZ. The intensity of oxidative stress was reduced by MK. (fig. 1).

The weight of the animals in the control group increased significantly after eight weeks. The weight of the animals in the group that received only MK also increased significantly compared to the weight at the beginning of the experiment. The weight of the STZ-only group decreased significantly after 8 weeks (initial weight249.3+/-18.1g vs.176.2+/-22.7g after 8 weeks p<0.01)



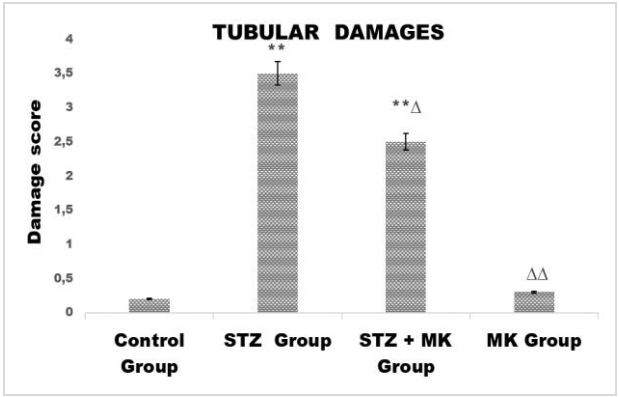
*p<0.05vs. Control, **p<0.01vs. Control, Δp<0.05vs. STZ, ΔΔp<0.01vs. STZ

Fig. 1: MDA plasma concentrations after 8 weeks.



*p<0.05vs. Control, **p<0.01vs. Control, Δp<0.05vs. STZ, ΔΔp<0.01vs. STZ

Fig. 2: Scored glomerular damages after 8weeks.



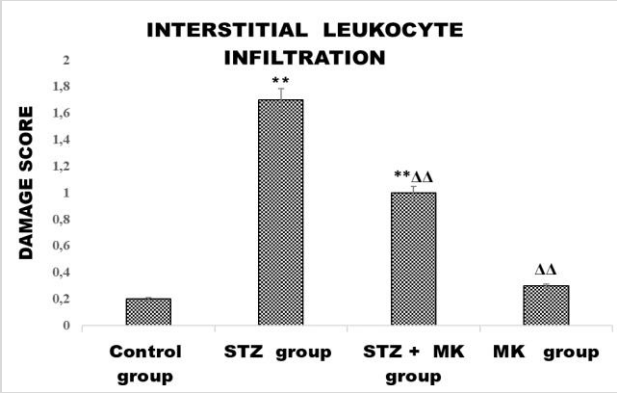
*p<0.05vs. Control, **p<0.01vs. Control, Δp<0.05vs. STZ, ΔΔp<0.01vs. STZ

Fig. 3: Scored tubular damages after 8weeks

Administration of MK to the group receiving STZ reduced the weight loss caused by diabetes (table 2).

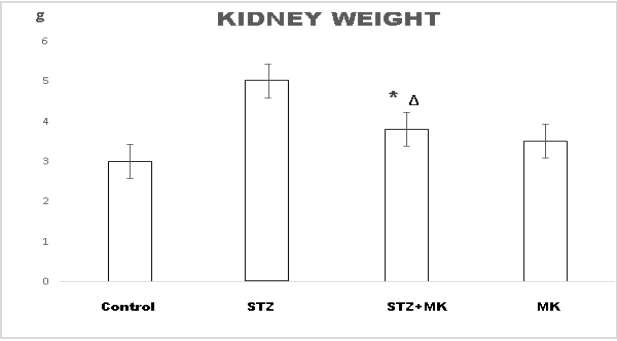
Diabetes severely affected the renal glomeruli. Administration of MK to the group receiving STZ reduced the intensity of glomerular damage caused by diabetes (fig. 2).

The tubular score was significantly lower in the diabetic group that received MK compared to the group that received only STZ (fig. 3).



*p<0.05vs. Control, **p<0.01vs. Control, Δp<0.05vs. STZ, ΔΔp<0.01vs. STZ

Fig. 4: MK influence on kidney interstitial leukocyte infiltration**.**



*p<0.05vs. Control, **p<0.01vs. Control, Δp<0.05vs. STZ, ΔΔp<0.01vs. STZ

Fig. 5: Variations in rats kidney weight after 8 weeks.

Leukocyte infiltration is increased in STZ-induced diabetes. Administration of Mk reduces this leukocyte infiltration. In the group receiving only MK there are no significant differences in leukocyte infiltration compared to the control group (fig. 4).

The kidney weight of animals with diabetes in the third group is significantly higher after 8 weeks than the kidney weight in the control group. MK reduced this weight gain of the kidneys of alleles with diabetes (fig. 5). In all the studied renal lesions (glomerular, tubular or interstitial), MK significantly reduces but does not suppress the production of lesions by diabetes.

In the group of rats that received only MK, there were no significant changes compared to the control group.

DISCUSSIONS

Leukotrienes are involved not only in pathology of bronchial asthma but also in other important human diseases. These lipid autacoids are involved in the pathogenesis of complications of diabetes such as diabetic retinopathy (Behl *et al*., 2016, Bapputty *et al*., 2019), heart disease and vascular damages (Colazzo *et al*., 2017) and others.

Diabetes mellitus is characterized by a high level free radicals generation. An increased oxidative stress is essential for promoting diabetic complications. Oxidative stress plays a central role in the production and development of diabetic nephropathy. Reactive oxygen species (ROS) upregulate transforming growth factor-beta 1 stimulates protein synthesis in mesangial cells and mesangial expansion (Ha and Lee 2001, Zhang *et al*., 2020).There is a complex relationship between TGF-1 beta and leukotrienes. Inhibition of 5-LO with zileuton or blocking cys LT1 receptors with MK reduces the effect of TGF-1beta on stimulating cell migration. On the other hand, TGF-β 1 increased 5-LO expression and the production of CysLTs and up-regulated CysLT1R (Huang *et al*., 2012).

Hyperglycemia induces inflammatory and profibrotic reactions, which are manifested pathologically as excessive deposition of extracellular matrix (ECM) in the glomerular mesangium, glomerular basement membrane thickening and tubular atrophy, ultimately leading to glomerulosclerosis and renal fibrosis. Other lesions found in experimental rat diabetes but also in human diabetes are: mesangial expansion, enlargement of the glomeruli, interstitial leukocyte infiltration.

Mesangial proliferation is also important in the pathogenesis of diabetic nephropathy. LTs are also proinflammatory agents and enhance free radicals formation. In diabetes, the level of proinflammatory cytokines (IL-1β, IL-6, TNF-α and TGF-β) in the kidneys is significantly higher compared to the normal kidney (Cao *et al*., 2021). Elevated levels of Il-6 and TNF alpha have been observed in experimental albumin-induced renal tubular lesions. This increase was not occurs in 5-LO (- / -) mice. Leukotrienes increase also interleukin 1 production by human monocytes.

Hyperglycemia in human or experimental diabetes determines the glycation of proteins and lipids and the formation of advanced glycation end-products. These compounds increase the synthesis of proinflammatory interleukins and TNFalpha in diabetes.In experimental studies, leukotriene antagonists such as MK866 attenuated oxidative stress while inhibiting proinflammatory cytokine production and reducing kidney damage (Hadi *et al*., 2011).

Table 1: Plasma glucose concentrations in all animals groups.

Group	Control	STZ	p*	p**	STZ+MK	p*	p**	MK	p*	p**
Initial	103±17	109±14	NS		105±12	NS	NS	107±9	NS	NS
After 72h	95±9	301±26	<0.01		293±10	<0.01	NS	110±12	NS	<0.01
After 8 weeks	107±11	387±22	<0.01		311±18	<0.01	NS	115±19	NS	<0.01

Initial= Prior to administration of any substance. All concentrations are expressed in mg/dl.
p*= p versus control group; p** =p versus STZ only group

Table 2: Influence of MK on the weight of animals with diabetes

Group	Initial weight (g)	After 8 weeks Weight(g)	p	p*
Group I (Control group)	253.5±12.2	327.3±21.5	<0.01	
Group II (STZ group)	249.3±18.1	176.2±22.7	<0.01	<0.01
Group III (STZ+MK)	251.6±14	210.4±16.1	<0.05	<0.01
Group IV (MK)	244±7.04	294.3±23.3	<0.05	NS

p versus initial weight ; p* versus control group;

There are data showing that MK reduces the level of proinflammatory cytokines such as TNF alpha and IL1 beta and increases the level of anti-inflammatory cytokines such as IL-10 (Khodabakhsh *et al*., 2022). There are cysLT1 receptors in mesangial cells and leukotrienes are involved in the proliferation of mesangial cells (McMahon *et al*., 2002, Yan *et al*. 2019). Leukotrienes mediate also apoptosis in renal tubular epithelial cells (Yang *et al*., 2011).

By inhibiting free radicals generation LTs receptors antagonists like MK could be involved also in renoprotection. There are data showing that MK has favorable effects in other pathological situations besides asthma and asthmatic bronchitis. But the possible therapeutic application of MK in the future is much wider than these two diseases.There are promising data regarding the possibility using leukotriene antagonists in the treatment of pulmonary hypertension, myocardial infarction (Hoxha *et al*., 2021) and the prophylaxis of atheromatosis. Our data show that MK significantly reduces but does not suppress glomerular and tubular lesions in experimental diabetes.

Our results are in agreement with the other experimental data showed that MK reduced sepsis-induced renal injuries, amikacin induced renal damages, cyclosporine experimental nephrotoxicity (Atakan *et al*., 2008, Helmy *et al*., 2018), doxorubicin-induced acute kidney damage (Kose *et al*. 2019), ın renal ıschemia (Aydin *et al*.2020)and metotrexat experimentally induced damages (Abdel-Raheem and Khedr 2014).

As in the case of experimental intoxication with doxorubicin, the results of this study also show that the protection given by MK against glomerular lesions is significant, but it is partial and not complete. In both cases, the protection is associated with the significant reduction of oxidative stress. In experimental renal ischemia in which, similarly to diabetes, the production of pro-inflammatory cytokines, synthesis of peptidoleukotrienes and oxidative stress are increased, MK reduced renal lesions and leukocyte infiltration caused by ischemia-reperfusion (Aydin *et al*. 2020)

Some experimental data indicate also the possibility of effective therapeutic use of MK in other diseases such as: gastric ulcer, focal cerebral ischemia (Yu *et al*., 2005), some pyelonephritis and others. A selective antagonist of cysLTs1 receptors, zafirlukast, has diminished the effect of Advanced Glycation End-Products on renal mesangial cells (Yan *et al*., 2019).

Inhibition of LTC4 action reduces oxidative stress. This could be a major mechanism for reducing diabetic kidney damage by MK. There are data that show that MK promotes glucose-stimulated insulin secretion (Guo *et al*., 2018), but our data showing that MK does not change the concentration of plasma glucose.

The results obtained by us are in agreement with the data which shows a small reduction in glucose levels in the animal group that received only MK, but in our experiment this reduction was not statistically significant.

Our data are consistent with other findings showing that MK reduced MDA levels in animals with increased oxidative stress and also with the data showing that MK decreased chronic renal failure-induced multiple-organ injury in rats (Sener *et al*., 2007).

CONCLUSION

Daily administration of MK in animals with experimental diabetes reduces all diabetic renal lesions. The protection given by MK is not complete but it is significant against glomerular and tubular lesions and against leukocyte infiltration. The reduction of diabetic lesions occurs at the same time as the reduction of oxidative stress.

We consider as a hypothesis, that MK would be useful in the treatment of chronic renal failure in diabetic patients. The administration of this peptidoleukotriene antagonist from the early stages of the disease could increase the therapeutic benefit.

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