The influence of smoking and comparison between ACE-I and ARB in the development and progression of diabetic nephropathy

Internal Medicine department
Omar Hamad, Medical Faculty, student 6th year
Supervisor: Edita Mašanauskienė
# TABLE OF CONTENTS

LITHUANIAN UNIVERSITY OF HEALTH SCIENCES (LSMU) .............................................................1

1. SUMMARY (ABSTRACT) .............................................................................................................4

2. SUMMARY (Lithuanian/Lietuvių k.) .....................................................................................6

3. ACKNOWLEDGMENTS ...........................................................................................................8

4. CONFLICTS OF INTERESTS .................................................................................................8

5. CLEARANCE ISSUE BY ETHICS COMMITTEE ....................................................................8

6. ABBREVIATIONS ....................................................................................................................9

7. INTRODUCTION ....................................................................................................................10

8. AIM AND OBJECTIVES .........................................................................................................12

9. LITERATURE REVIEW .........................................................................................................13

   9.1. The Nephron - structure and physiology ......................................................................13
   9.2. GFR changes measured by serum creatinine .................................................................14
   9.3. Normal GFR ....................................................................................................................15
   9.4. Diabetic nephropathy and its pathophysiology ............................................................15
   9.5. Clinical stages of diabetic nephropathy and GFR changes ................................................17
   9.6. Albuminuria – An important marker of diabetic nephropathy ......................................18
   9.7. Development of diabetic nephropathy induced by smoking .........................................19
   9.8. Different outcomes in smoking vs non-smoking in diabetic patients ...........................20
   9.9. Progression of diabetic nephropathy in type 1 and 2 diabetes: Smokers vs non-smokers 21
   9.10. Smoking - An independent risk factor .......................................................................21
   9.11. Mechanism of Angiotensin converting enzyme inhibitor (ACE-I) and Angiotensin receptor blockers (ARB) ..........................................................22
   9.12. ACE – I vs ARB: Differences in benefits ........................................................................24

   9.12.1. ACE inhibitor’s effect on diabetic patients .................................................................24
   9.12.2. Outcomes in patients treated by angiotensin receptor blocker (ARB) .....................25
   9.12.3. Combined therapy: ACE inhibitor and ARB ............................................................26
   9.12.4. ACE inhibitor versus ARB ......................................................................................27

10. RESEARCH METHODOLOGY ............................................................................................32

   10.1. Initial search and collection of information .................................................................32
   10.2. Assessment of eligibility ...............................................................................................32
   10.3. Inclusion criteria ...........................................................................................................32

11. RESULTS ............................................................................................................................34

   11.1. The risk of smoking .......................................................................................................34
11.1.1. The study of Rabi et al (Aleppo) ............................................................................................34
11.1.2. The study of Hyungseon Yeom et al (Korea) ...........................................................................35
11.2. Outcomes differences: ACE-I vs ARB .........................................................................................36
  11.2.1 DETAIL trial ..............................................................................................................................36
  11.2.2. Meta-analysis by Jicheng Lv et al ............................................................................................37
12. DISCUSSION .......................................................................................................................................39
  12.1. The relation of smoking to diabetic nephropathy in diabetics .........................................................39
  12.2. Outcome comparison between ACE-I and ARB ............................................................................40
  12.3. The difference between dual therapy and monotherapy in diabetic patient .................................41
13. CONCLUSION .....................................................................................................................................43
14. REFERENCES .......................................................................................................................................44
1. SUMMARY (ABSTRACT)

Author: Omar Hamad; Supervisor: Dr. Edita Mašanauskienė

Title: The influence of smoking and comparison between ACE-I and ARB in the development and progression of diabetic nephropathy

Aim and objectives:
Aim: The aim of this research is to compare the effects and outcomes between smokers to non-smokers in relation to onset and progression of diabetic nephropathy and the outcome changes in patients treated by ACE-I compared to those treated with ARB.

Objectives:

• To compare several literature data in the changes of urinary albumin in smokers and non-smokers
• To study the changes in serum creatinine, GFR changes and rate of ESRD comparing smokers to non-smokers from different studies done earlier
• To investigate the impact of smoking behaviors (smoking only before diagnosis of diabetes and smoking any time after diagnosis of diabetes) and amount of cigarette exposure on urinary albumin, analyzed in previous studies
• To compare literature data in the risk of onset or progression in urinary albumin between individuals taking ACE-I and those taking ARB
• To investigate the serum creatinine changes, GFR changes and ESRD rate in both mentioned drug group by comparing earlier studies
• To compare the outcomes in dual therapy contra monotherapy demonstrated in other studies

This research was a meta-analysis, comparing the results on diabetic patients, which developed or showed increased risk for diabetic nephropathy. In total 25 references, 3 books and 22 articles, were used for our comparison and review. Inclusion criteria was relatively broad and contained: diabetic patients (regardless type, sex and gender). The later studies collected were those focusing on outcomes based on urinary albumin, serum creatinine changes, GFR and ESRD rates.

In our results we directed the focus on four main studies (two related to the risk of smoking and two comparing ACE-I to ARB).
Summarized conclusion:
1. Smoking is a definitive, major risk factor of diabetic nephropathy progression.
2. Smoking is an independent risk factor, in which the risk escalates with the increasing amount of cigarettes smoked and behavior of smoking documented (smoking after diagnosed diabetes).
3. Majority of the studies favored ACE-I in prevention of diabetic nephropathy and its progression, though the studies reviewed had different factors that could bias the results. A larger group of patients in discussed studies were treated by additional antihypertensive medications, which could be a major factor to influence the results.
4. In addition, major risk factors and concomitant disease were not greatly taken into consideration and equally distributed. Therefore we cannot conclude greater efficacy in preventing development or progression in any of the drug groups.
2. SUMMARY (Lithuanian/Lietuvių k.)

Autorius: Omar Hamad; Darbo vadovas: Dr. Edita Mašanauskienė

Pavadinimas: Rūkymo, AKF-I ir ARB poveikio palyginimas diabetinės nefropatijos vystymuisi ir progresavimui

Tikslas: Literatūros apažvalgos tikslas yra palyginti rūkančių ir nerūkančių, vartojančių AKF-I arba ARB paveikį ir išeitis diabetinės nefropatijos vystymuisi.

Uždaviniai:

- Palyginti literatūros duomenys, kaip rūkymas įtakoja albuminų kiekį šlapime.
- Remiantis anksčiau atliktais tyrimais įvertinti rūkymo įtaka kreatinino koncentracijai serume, glomerulo filtracijos greičiui ir terminalinės inkstų ligos vystymuisi
- Įvertinti rūkymo poveikį ir surūkytų cigarečių kiekio įtaką albuminų kiekio šlapime
- Palyginti literatūros duomenis kokią įtaka albuminurijai atsirasti ar progresuoti turi AKF-I ar ARB vartojimas pacientas
- Palyginti anktesnių tyrimų duomenis, kaip minėtos vaistų grupės įtakoja GFG pokyčius bei terminalinės inkstų lygos vystymąsi
- Palyginti galimas baigtis vartojant viena ar abu medikamentus kartu

Šis tyrmas – metaanalizė, lyginanti diabetų sergančių pacientų rezultatus, kuriems padidėjo rizika, išsivystė arba pasireiškė diabetinė nefropatija. Naudotos 25 nuorodos, 3 knygos, 22 straipsniai. Medžiaga buvo analizuojama ir lyginama, Visi pacientai buvo sergantys cukriniu diabetu, Pacientai buvo įvairaus amžiaus , lyties ir rasių. Albuminurija , serumo kreatinino pokyčiai, GFG ir terminalinis inkstų ligos pažeidimas yra pagrindinis naujausių studijų tyrimo abjektas

Šioje tyrimų apžvalgoje daugiausiai dėmesio skyriaus 4 pagrindinės tyrimams(2 susijusiems su rūkymo rizika ir 2 lyginantiems AKF –I ir ARB vartojusius pacientus.
Išvados:

1. Rūkymas yra pagrindinis diabetinės nefropatijos progresavimo rizikos veiksnys.

2. Rūkymas yra nepriklausomas rizikos veiksnys, kurio sukelia rizika didėja, kai surūkoma daugiau cigarečių ir kai ligonis toliau rūko net ir po ligos diagnozavimo.


3. ACKNOWLEDGMENTS

Alhamdulilah, all praise is due to Allah, The Almighty, for his blessings of giving me good health and ability to finish this work peacefully.

I would like to express my deepest gratitude to my supervisor Dr. Edita Mašanauskienė. Her essential advises and continuous support were outstanding. The author is thankful for having an extraordinary supervisor, with remarkable patience and encouragement.

I would also like to acknowledge enormous appreciation to Jeanie Jafari for her valuable comments, knowledge and opinions. Her effort in checking and editing was incredible.

I reward a special thank for my brother Mahmoud Hamad for his technical and statistical support. His invaluable guidance and assistance made it possible to complete this research.

Last but not least, my greatest love go to my family who always been next to me throughout life and during my studies. Without them I would not been here today, successfully ending 6 years of medical studies.

4. CONFLICTS OF INTERESTS

There were no conflicts of interests.

5. CLEARANCE ISSUE BY ETHICS COMMITTEE

For this research we didn’t need permission from ethical committee. The data presented were not our own results. The numbers and statistics presented were from earlier studies done.
6. ABBREVIATIONS

ACE-I – Angiotensin converting enzyme inhibitor
ACR – Albumin-creatinine ratio
ARB – Angiotensin II receptor blocker
BP – Blood pressure
CKD – Chronic kidney disease, also known as chronic renal failure
DM – Diabetes mellitus
DN – Diabetic nephropathy
ECM – Extracellular matrix
ESRD – End stage renal disease
GBM – Glomerular basement membrane
GFR – Glomerular filtration rate
IDDM – Insulin dependent diabetes mellitus
NIDDM – Non-insulin dependent diabetes mellitus
UAE – Urinary albumin excretion
7. INTRODUCTION

Diabetic nephropathy, a complication of diabetes is the leading cause of CKD. The deterioration of the renal function is different between individuals, but according to previous studies several factors could impact the progression or even the regression. These studies mainly directed their focus on changes of albumin in the urine, changes of creatinine and GFR. Albuminuria has been shown to be an important marker of renal injury and therefore must be taken into consideration when evaluating the function of the kidney. According to the last guidelines and studies albuminuria appears 5-10 years after onset of diabetes. Albumin is a small protein that normally shouldn’t be filtrated by the glomerulus, which is the filtration and functional unit of the kidney. The negatively charged GBM repel the albumin which also is a negatively charged structure. In a hyperglycemic state, the excess of blood glucose generates the free radicals which damage this membrane, making the filtration of this protein possible.

Creatinine clearance, usually considered the same as GFR, is another essential marker of kidney function. Regardless of disease, the creatinine clearance always reflects the state of the kidney and no matter the underlying cause, a decrease mainly signals deterioration in renal function.

For the last decades the impact of smoking on diabetic nephropathy and its progression has been analyzed in many studies. Smoking has been demonstrated to increase the free radicals, thereby increasing the damage to the kidneys. In diabetes, both types 1 and 2, smoking has been shown to be a main risk factor of kidney deterioration. The amount and behavior of smoking played an important role, when reviewing earlier studies.

According to latest studies, both important markers, urinary albumin and GFR, have been highly influenced by smoking.

In earlier studies, the treatment and prevention of diabetic nephropathy was also widely discussed. The main important question regarding the treatment has been whether to choose ACE-I or ARB for diabetic patients. Data of previous studies reflect the outcomes of these medications differently and the results vary widely. ACE-I could be highly favorable in several studies, while in other studies ARB has been considered to be more effective. Later on in this meta-analysis, the last results from other researches will be demonstrated and the impact of ACE-I as opposed to ARB. Urinary albumin, creatinine clearance and adverse effects will be compared between the two drug groups.
Beneficial effects from dual therapy has in some cases been more beneficial compared to single therapy by one of the drug groups. This treatment is not used nowadays, and the reason will also be explained in the literature review.
8. AIM AND OBJECTIVES

**Aim:** The aim of this literature review is to compare the effects and outcomes between smokers to non-smokers in relation to onset and progression of diabetic nephropathy. The second aim is to compare the outcome changes in individuals taking ACE-I compared to those taking ARB, by reviewing different studies.

It is essential to investigate the relation and changes in risk of smoking on diabetics, particularly those with diabetic nephropathy. Previous studies showed that smoking is one of the main risk factors for this complication of diabetes. Recent studies also showed different results in the outcomes (occurrence and progression) for ACE-I compared to ARB in diabetics. Several studies have also compared dual therapy against monotherapy (ACE-I or ARB), which also will be done in this meta-analysis.

**Objectives:**

- To compare several literature data in the changes of urinary albumin in smokers and non-smokers
- To study the changes in serum creatinine, GFR changes and rate of ESRD comparing smokers to non-smokers from different studies done earlier.
- To investigate the impact of smoking behaviors (smoking only before diagnosis of diabetes and smoking any time after diagnosis of diabetes) and amount of cigarette exposure on urinary albumin, analyzed in previous studies
- To compare literature data in the risk of onset or progression in urinary albumin between individuals taking ACE-I and those taking ARB
- To investigate the serum creatinine changes, GFR changes and ESRD rate in both mentioned drug groups by comparing earlier studies
- To compare the outcomes in dual therapy contra monotherapy demonstrated in other studies
9. LITERATURE REVIEW

9.1. The Nephron - structure and physiology

The anatomical and physiological properties of important structures found in the kidneys of the human body are discussed in Ganong by Kim Barrett et al.

The structural and functional unit of a kidney is called a nephron, which contains glomerulus and renal tubule. Each kidney in our body contains approximately 1,3 million nephrons. [1]

The structure of the glomerulus

The glomerulus is a filtration unit of the nephron that is formed by a tuft of capillaries invaginated in the center. These capillaries are supplied by afferent arteriole and drained by the efferent arteriole at its distal end.

In the glomerulus, the filtration occurs through the filtration barrier. In Ganong by Kim Barrett et al the barrier is explained, consisting of three layers:

1. Fenestrated endothelial cells of the capillaries (with pores that are 70-90 nm)
2. Podocytes (specialized epithelium) and
3. Glomerular basement membrane (GBM) lying in between those two layers mentioned before.

*Podocytes have numerous pseudopodia (foot-like processes) that interdigitate to form filtration slits along the capillaries. Those slits are about 25 nm wide and closed by a thin membrane. [1]

In the article of Abrahamson DR the GBM, the basal lamina, is explained structurally, emphasizing importance of it and its structures. Later on in this article it’s explained as extracellular matrix component of the glomerular filtration barrier. This is a selectively permeable barrier separating the vasculature from the urinary space (Bowman’s space). GBM is composed of laminin and collagen that is crucial for its structure and function. The membrane does not have any visible gaps or pores. [2]

Ganong further discuss that between basal lamina (GBM) and the endothelium there are stellate cells, also known as Mesangial cells (similar to pericytes located in other areas of the body). These cells are typically located between two enclosed capillaries, and in these locations a sheath of basal membrane is shared between both capillaries. The mesangial cells are contractile and play an important role in the filtration
through the glomerulus. They are also involved in other functions like: secreting the ECM, taking up immune complexes, and being involved in progression of different glomerular diseases.

Physiologically, the filtration through the filtration membrane depends on: (1) size and (2) charge of molecule, according to Kim Barrett et al in Ganong. Glomerular membranes allow the passage of neutral substances up to 4 nm in diameter and inhibit almost totally the passage of substances greater than 8 nm. (4-8 nm possible to be filtered, although not freely filtered)

Both red blood cells and white blood cells are too large to be filtered through the filtration slits. Neutral substances less than 4 nm are freely filtered.

Negatively charged sialoproteins in the glomerular capillary wall repel negatively charged substances in the blood that otherwise could be possible to be filtered according to their size. This explanation could be given to albumin filtration. Albumin is a protein with a size of 7 nm, which by its size alone would be possible to be filtered. However glomerular concentration of albumin is only 0.2 % of its plasma concentration. Impact of the negative charge that this molecule contains causes it to be repelled back to the plasma almost completely. [2]

9.2. GFR changes measured by serum creatinine

Experiments were done on animals and humans to measure glomerular filtration rate (GFR) as accurate as possible, Ganong stated. Those experiments showed that GFR is most accurately measured when the determined substance is freely filtered by the glomeruli. In order to have the measurement accurate, this substance must neither be secreted nor reabsorbed by the renal tubules.

After several experiments, the optimal substance for this accurate measurement was inulin (a polymer of fructose). Inulin is a substance also that is nontoxic and not metabolized by the body, which is preferred. This polymer is injected parenterally, first as a loading dose, then as a sustaining intravenous dose. Later on, accurate urine specimen is collected and plasma sample taken halfway by accurate specimen. The last process mentioned is done after inulin has been equilibrated with body fluids.

The formula used to measure the GFR by this method:

\[ \frac{U \times V}{P} \]

U=Urine concentration of the substance
V= Urine flow per unit of time
P= Arterial plasma concentration of the substance (Same in all parts of arterial circulation)
The physiology of creatinine clearance was explained in Ganong and is an important aspect to understand GFR estimation. Creatinine is secreted and some reabsorbed by renal tubules, but creatinine clearance ($C_{Cr}$) could also be used to determine the GFR. In addition to the secretion and reabsorption in the tubules, plasma creatinine determinations are inaccurate at low levels (because the method determining creatinine levels also measures other plasma components of small amount).

Clearance of endogenous creatinine despite this fact is frequently used as a method. Due to the tubular secretion, the urine concentration of creatinine ($U_{Cr}V$) is high. Plasma concentration of creatinine ($P_{Cr}$) is also high because of nonspecific chromogens. High $U_{Cr}V$ with concurrent high $P_{Cr}$ tend to cancel out these errors. [2]

### 9.3. Normal GFR

Later on, in the same chapter, it was mentioned that normal GFR in a healthy individual is in average 125 ml/min. Values are 10 % lower in women than in men. This normal GFR value is in a person with a normal urine volume of about 1L/d. From the filtrate 99 % or more is normally being reabsorbed. During one day our kidneys filter equal to 4 times our total body volume, 15 times the ECF volume and 60 times the plasma volume. [1]

### 9.4. Diabetic nephropathy and its pathophysiology

According to Radica Z. A. et al, in an article published May 2017 diabetic nephropathy is the leading cause of CKD in the US but also worldwide. This disease develops as a complication in around 30 % of patients with type 1 DM and around 40 % of patients with type 2 diabetes mellitus. For the last few years the incidence of diabetic nephropathy in the US has increased.

Not all patients with diabetes develop nephropathy. Up to 40 % of diabetic patients develop this complication. The reason why it doesn’t develop in all diabetic patients is not fully known yet. [3]

Histological changes in diabetic nephropathy are described by Vecihi Batuman et al as following:

1) **Mesangial expansion** – Caused by hyperglycemia (which is probably caused by increased matrix production/glycation of matrix protein)
2) **Glomerular basement membrane (GBM) thickening**
3) **Glomerular sclerosis**
Earliest morphological alteration in the diabetic nephropathy is the GBM thickening and mesangial expansion caused by accumulation of the extracellular matrix. [4]

Many studies showed that hyperglycemia in combination with genetic predisposition, particularly in the metabolism of glucose, are the key factors of the morphological alterations in diabetic nephropathy. Increase of glucose uptake and generation of free radicals has been shown in several structures of the kidney. These structures are mainly epithelial cells, mesangial cells and proximal tubular epithelial cells.

There is evidence according to S. O. Kolset et al, which shows that all components of the kidneys are exposed to hyperglycemia. Main and primary injury is in glomerular tuft, increasing mesangial volume but also disrupting the basement membrane integrity. Both of these mentioned changes subsequently lead to glomerular leakage of albumin and gradual decline in renal function. [5]

Josephine M. Forbes et al described the changes of diabetic nephropathy more widely. The changes were explained as following:

1) **Mesangial expansion**

Hyperglycemia induces an increase of intracellular ROS and other free radicals which then cause injury to the mesangial cells in the glomeruli. Mesangial cells, as earlier mentioned, are capable of secreting ECM. Thus, explaining the result of increased ECM is the mesangial expansion.

Another pathway by which the mesangial expansion could be caused is the glycation of the matrix protein. When a large amount of glucose is present, by activation of the polyol pathway, there is activation protein kinase C (PKC) and formation of advanced glycation end products (AGEs), making the collagen in the matrix more resistant to degradation.

2) **Basement membrane thickening**

Due to the effect of hyperglycemia there is increased generation of AGEs and therefore also ECM and plasma proteins are affected. Collagen type IV present in BM is thought to be glycated in patients with diabetic nephropathy. This further increases the resistance to proteases, contributing to the thickening of the basement membrane in the glomeruli.

3) **Glomerular scleroris**

With the progression of DN, glomerular sclerosis occurs. The reason for this is the massively accumulated components of the ECM in the mesangium at the expense of the capillary volume. Further on, hyaline atherosclerosis has been shown in patients with this complication of diabetes. [6]
In Harrison, 19th edition, it is explained by Dennis L. Kasper et al that GBM composition is also altered noticeably with the loss of heparin sulfate moieties. It is a negatively charged molecule and therefore also it repels other negatively charged molecules in the blood. Molecules being repelled (for example albumin) are not filtered, or filtered to a smaller extent. The change of this structure mentioned in the GBM increases the filtration of serum proteins into the urine, predominantly charged albumin.

It is further mentioned in Harrison’s that the degree of glomerular hyper filtration is correlated with clinical significant nephropathy risk. From the diabetic patients that develop diabetic nephropathy around 40% have increase in albuminuria as earliest finding. A range of 30-300 mg/24 h of albumin in urine is called microalbuminuria. Nowadays it’s recommended to test patients with type 2 diabetes for albuminuria at time of diagnosis and thereafter yearly.

With continuous increase in albuminuria, urinary albumin later reaches a positive dipstick proteinuria level (>300 mg albuminuria). The positive dipstick proteinuria usually occurs 5-10 years after onset of early albuminuria. Overt nephropathy contains variable amounts of proteinuria, ranging between 500 mg – 25 g/24h. [7]

9.5. Clinical stages of diabetic nephropathy and GFR changes

An article done in South Africa by M.R Moosa et al divided the clinical stages of diabetic nephropathy into five stages. Clinical correlation between GFR and urinary albumin excretion (UAE) and stages of diabetic nephropathy explained in this table below (Table 1):

<table>
<thead>
<tr>
<th>Table 1. Stages of Diabetic nephropathy [9]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>1. Hyperfiltration</td>
</tr>
<tr>
<td>2. Microalbuminuria</td>
</tr>
<tr>
<td>3. Overt proteinuria</td>
</tr>
<tr>
<td>5. ESKD</td>
</tr>
</tbody>
</table>

ESKD = end stage renal disease; GFR = glomerular filtration rate; UAE = urinary albumin excretion.
Regardless of etiology, CKD is mostly divided into five different stages based on estimate GFR value. Those stages could be found in the article of Robert Thomas et al. The 5 stages are as follows:

- Stage 1: normal eGFR ≥ 90 mL/min per 1.73 m² and persistent albuminuria
- Stage 2: eGFR between 60 to 89 mL/min per 1.73 m²
- Stage 3: eGFR between 30 to 59 mL/min per 1.73 m²
- Stage 4: eGFR between 15 to 29 mL/min per 1.73 m²
- Stage 5: eGFR of < 15 mL/min per 1.73 m² or end-stage renal disease [9]

9.6. Albuminuria – An important marker of diabetic nephropathy

As previously mentioned in this review, increased albumin in the urine points to damage of the glomerular filtration membrane. Albuminuria or microalbuminuria is usually determined by urinary albumin of ≥30 mg/24 hours or albumin/creatinine ratio (ACR) ≥30 mg/g (≥3 mg/mmol). This determination of microalbuminuria is according to a study published 2016 by Ki-Chul Sung et al. Microalbuminuria is particularly used as a marker of damage to the kidney, and along with low estimated GFR (eGFR) defines chronic kidney disease. More than being just a predictor of progression of diabetic nephropathy and nondiabetic renal diseases, albuminuria also signals that there is endothelial dysfunction going on. [10]

Supporting these mentioned facts, Harrison also define microalbuminuria as albuminuria between 30 and 300 mg/24h. This finding (detected by immunoassay) is usually the earliest manifestation in patients who develop diabetic nephropathy in 40 % of the cases. 5-10 years after onset of diabetes, microalbuminuria usually develops. Furthermore Harrison´s in the same chapter discuss the differences between type 1 and type 2 diabetes and their relation to diabetic nephropathy. While type 1 diabetes is easily identifiable at its onset, type 2 diabetes is usually silent in its progression and patients may present with advanced diabetic nephropathy when newly diagnosed with diabetes. Renal hypertrophy and glomerular hyper filtration has already occurred at the time of onset of diabetes. The risk of clinical significant nephropathy is highly dependent on degree of glomerular hyper filtration. 5 years after diagnosis it is recommended to test patients for microalbuminuria - thereafter yearly in type 1 diabetics. Because of the rapid progression, type 2 diabetics should be tested for microalbuminuria at time of diagnosis and thereafter yearly. Positive levels of proteinuria on the urinary dipstick occur 5-10 years after onset of early diabetic nephropathy. Later on,
patients may progress to outright diabetic nephropathy which varies in the amount of urinary albumin, ranging between 500 mg – 24 g/24 h, according to Harrison’s [7].

9.7. Development of diabetic nephropathy induced by smoking

Chakkarwar VA in his review discussed about the possible effects of smoking in diabetic nephropathy. It’s thought that smoking results in free radicals and pro-oxidant molecules development. It has also been shown to cause adverse influence on endothelial cells by an inhibitory effect on components of L-arginine-nitric oxide pathway. Moreover, by decreasing the NO bioavailability nicotine plays a key role in endothelial dysfunction. This is caused by mediating high oxidative stress with low availability of nitric oxide synthase, explaining the decreased generation and bioavailability of nitric oxide, thereby influencing the progression of diabetic nephropathy by this pathway. Previous studies, done by David et al, and reviewed by Chakkarwar VA, showed that progression of diabetic nephropathy is worsened by smoking as it increases both the severity of ECM deposition and the expression of profibrotic cytokine TGF-β. Nicotine has also been seen to increase generation of superoxide, which is a result of activation of NADPH oxidase and PKC.

Another important mechanism explains the effect of smoking on lipids. This mechanism shows that lipid accumulation occurs by increasing expression of SREBP-1, a process stimulated by smoking. SREBP-1 is responsible for increasing synthesis of TGs and cholesterol, which is also another essential contributor in progression of diabetic nephropathy.

This figure below summarizes the different contributors of the damage to kidneys and progression of diabetic nephropathy (Figure 1)

![Figure 1. Pathogenesis of smoking related damage](image-url)
TGF-β: Transforming growth factor β; PKC: Protein kinase C; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; SREBP: Sterol regulating element binding protein; VED: Vascular endothelial dysfunction. [12]

9.8. Different outcomes in smoking vs non-smoking in diabetic patients

One of the most sensitive markers of glomerular injury is urinary albumin. Relations between smoking and albuminuria have been done in several studies where albuminuria has been seen to directly or indirectly induce renal damage. According to Mimran et al, discussed by Rabi Yacoub et al, microalbuminuria was detected with double the frequency in smokers as that in non-smokers. The risk of attaining a smoking related end stage renal disease (ESRD) was increased to 1.69x and was not related to conditions such as age, ethnicity, blood pressure, serum cholesterol and income. [12]

Rabi Yacoub, et al reported that smoking has been shown to cause a collection of kidney anomalies that relate to albumin excretion. It has been shown to:

1. Decrease the period between the start of diabetes and that of proteinuria or albuminuria, in other words, increase the risk of albuminuria development.
2. In addition, it has also been shown to accelerate the rates of progression from microalbuminuria to persistent proteinuria.
3. Furthermore it has been shown to increase the rate of transformation from diabetic nephropathy to ESRD. In a study involving 359 young adults with IDDM, Chase et al discovered that borderline (> 7.4 mcg/min) and abnormal (>30 mcg/min) albumin excretion was significantly (around 2.8x) higher in smokers than that in those who didn’t smoke. In another study, Sawicki concluded that odds of progression from a state of diabetic nephropathy to end stage renal disease was increased by a factor of 2.74 for each 10 pack/year smoking history. Biensenbach revealed on a similar note in his study how the GFR decline rate was elevated by 1.44 times in smoking patients relative non-smokers and were in an insulin dependent diabetes mellitus state (IDDM) whereas up to 1.66 times in those with a non-insulin dependent diabetes mellitus state (NIDDM). [12]

In regards to the impact that stopping smoking has on kidney function, Chase discovered that when smoking was stopped, albuminuria began to diminish greatly. In another study done by Sawicki, mentioned by Rabi Yacoub et al, also conducted on the same matter, a progression of nephropathy was less among smokers (around 11% of his studied subjects) while around 53% in those who smoked and not surprisingly 33% in those who had quit smoking. In addition, his study concluded a direct relation between pack/year smoking and progression of diabetic nephropathy. [12]
9.9. *Progression of diabetic nephropathy in type 1 and 2 diabetes: Smokers vs non-smokers*

E. Ritz et al. in their review mentioned the study done under Biensenbach et al, which evaluated the difference in the change of GFR between smokers and non-smokers with Type 1 diabetes. GFR loss was 1.44 times higher in smokers compared to non-smokers in type-1 diabetes. [14]

As in type 1 diabetes, progression of GFR decline in type 2 diabetes was also showed to be higher in smoking patients. A 5-year follow-up by Temduang Chuahirun et al compared the rate of GFR decline comparing smokers against non-smokers. Several risk factors like smoking and BP effect were evaluated. Cigarette smokers showed to have 2 times higher risk of decrease in GFR compared to non-smokers. The only examined factor which predicted the progression of DN was smoking. The greater decrease of GFR in smokers was despite the therapy by ACE-I and good control of BP. Similar results could be noted in the study of Hyungseon Yeom [13, 15] (Figure 2)

![Figure 2. GFR changes in smokers vs non-smokers in type 2 DM](image)

9.10. *Smoking - An independent risk factor*

A study done by Pinto-Sietsma et al, reviewed by Stephan R et al, involved 7476 participants in PREVEND trial. After adjustment of possible associated risk factors, they drew a correlation between cigarette smoking and urine albumin concentration. Clearly, it was shown that smoking increased the risk for presence of increased urinary albumin concentration, whether the patient smoked <20 or >20 cigarettes per day (relative risk [RR] 1.33 and 1.98, for both groups respectively).
28,409 volunteers from general population under a study of Halimi et al, another study also reviewed by Stephan R et al demonstrated that:
- Current and former smokers had significant risk for macroalbuminuria (adjusted RR 3.26 and 2.69 respectively)

Later on, Stephan R et al in his work discussed a cohort study done by Bleyer AJ et al, which analyzed how kidney function could be related to smoking. This study was done on 4142 nondiabetic participants, which had adjustments to other potential associated factors that could influence the results. However, the results from this study showed that number of cigarettes per day markedly influenced the progression of CKD. The risk of elevated serum creatinine ≥27 μmol/L during a minimum of three years was increased by 33% for every 5 cigarettes smoked per day. [16]

For many years different studies have been done worldwide where the effect of smoking on kidneys has been analyzed.
In Japan a 10-yr follow up study was done which involved 123,764 individuals with an age >40 yr. During that study it was found that in both men and women smoking was an important risk factor of CKD (RR measured for CKD stage 3 to 1.13 and stage 4 to 1.16). Another study (cross-sectional) was also performed in Norway mentioned by Stephan R et al, which involved 65,193 individuals. There was no difference in men and women and for both genders there was a dose-dependent increased risk of CKD (GFR <45 ml/min per 1.73 m²) with lifetime cigarette smoking of at least 25 pack-years (adjusted RR 1.42 for 25 to 49 pack-years and 2.05 for >50 pack-years, respectively). Apart from the risk of smoking >25 pack-years, obesity and physical inactivity also showed to increase the risk. Therefore interaction of these lifestyle risk factors still play a role and always need to be taken into consideration. Stephan R et al in his review also wrote about the study done on 2981 Italian individuals in the age range between 65 and 84 yr. The strongest independent risk factor of pathological renal function decline was current smoking with >20 cigarettes per day (odds ratio 2.3) [16]

9.11. Mechanism of Angiotensin converting enzyme inhibitor (ACE-I) and Angiotensin receptor blockers (ARB)

Independent from their systematic antihypertensive effect, in several large trials they were shown to slow the diabetic nephropathy progression according to Harrison, 18th edition volume 2. Slowing of the
progression can both be seen in early stages (microalbuminuria) and later (proteinuria with reduced GFR). Majority of patients with diabetic nephropathy require at least three antihypertensive medications. [1]

The mechanism of both ACE-I and ARBs are discussed by Bertram G. Katzung et al in Basic and Clinical pharmacology ACE-I is a class of drug that inhibit peptidyl dipeptidase enzyme (which hydrolyze angiotensin I to angiotensin II and inactivates a strong vasodilator, bradykinin). By the action of improved intrarenal hemodynamics and the decrease in resistance of efferent arteriole this group of medication decreases the proteinuria but also stabilizes renal function (even without the BP decrease). Therefore, ACE-I play an essential role in treatment of chronic kidney disease (as in diabetes). The second group of medications, ARB, block type I receptors of angiotensin II resulting in vasodilation (including systemic blood vessels and efferent arteriole of the glomerulus). ARB also by the angiotensin II blockade decreases aldosterone secretion. Bertram G. Katzung et al explains that ARBs are potentially stronger compared to ACE-I in providing a complete inhibition if angiotensin action. This is explained by the fact that angiotensin II can be generated by enzymes other than ACE-I. ARBs provide similar benefits to ACE in patients with chronic kidney disease. [17] (Figure 3)

![Figure 3. Summarized mechanisms of ACE-I and ARB](image-url)
Further on in Harrison Principles of Internal Medicine, 18th edition the use of these medications are discussed regarding treatment in type 1 or type 2 diabetes. Patients diagnosed with type 1 diabetes for five years, that progress to a state with microalbuminuria or a decreased renal function should be treated with ACE-I. Patients that have been diagnosed with type 2 diabetes with microalbuminuria or proteinuria are recommended to be treated either by ACE-I or ARBs. Rare evidences have been found that supports a combination of these two drugs. [1] (Figure 4)

9.12. ACE – I vs ARB: Differences in benefits

9.12.1. ACE inhibitor’s effect on diabetic patients

In previous studies, ACE inhibitors were shown to have a strong influence of slowing the progression of DN in both type 1 and type 2 diabetes. In Collaborative Study Group trial, discussed by Andy Kh Lim et al about type 1 diabetics, Captopril was shown to slow down the progression of albuminuria but also renal function deterioration. 409 type 1 diabetics, under the study of Collaborative Study Group trial, Captopril compared to placebo had a decreased risk of doubling serum creatinine by 48%. Treatment by Captopril also enabled continued remission of nephrotic-range proteinuria. Another study, also reviewed by Andy Kh Lim supported the study of Collaborative Study Group trial. The second study demonstrated that individuals who had remission (albuminuria <600 mg/day) for ≥1 year also showed better outcomes compared to the patients with no remission. Patients with remission had slower GFR deterioration and decreased risk of dialysis, transplantation or even death.

Andy Kh Lim in his article discussed about ADVANCE trial done on 11,140 patients with type 2 diabetes. After the use of perindopril/indapamide treatment in a follow up of 4.3 years the result showed a (1) decreased new onset of microalbuminuria, but also (2) prevented microalbuminuria to overt nephropathy progression. In this study serum creatinine was unchanged, and ESRD was not observed. Another trial mentioned by Andy Kh Lim was the BENIDICT trial, which also showed a delay in onset of microalbuminuria in type 2 diabetic using ACE inhibitors. These diabetic patients were with baseline normoalbuminuria but with hypertension. [18]

Jicheng Lv et al, in their meta-analysis, demonstrated changes of urinary albumin, serum creatinine doubling or occurrence of ESRD in both ACE-I and ARB. These will be showed later in our results. (Figure 12)
There were certain limitations for these studies, as the effect of agents that lowered the BP could not be ascertained. Direct Studies 2009, reviewed in the same article of Jicheng Lv et al, reported that diabetic patients also could show us a decreased renal function without albuminuria. According to Jicheng Lv et al GFR will not necessarily be normalized by prevention of albuminuria, meaning that development of kidney failure could occur even when preventing albuminuria by one or several medications. These facts, although earlier observational studies done demonstrated a strong relation between levels of albuminuria and risk of GFR reduction. [20]

9.12.2. Outcomes in patients treated by angiotensin receptor blocker (ARB)

The study earlier mentioned in this review, Jicheng Lv et al, reported that ARB had no significant effect on new onset microalbuminuria or macroalbuminuria compared to placebo or no treatment. The reviewed studies in their work however faced heterogeneity across different included studies. Recruited patients in reviewed studies by Jicheng Lv et al included patients with previous cardiovascular disease or other risk factors and type 2 diabetics rather than patients with type 1. These studies also included albuminuria with higher baseline risk of progression. [20]

Other three studies discussed in Giovanni FM Strippoli et al had a significant lower risk of progression from micro- to macro albuminuria with ARB. The decreased risk was calculated to 55% and between those three studies there was no significant heterogeneity. [21]

IDNT trial mentioned in the article by Andy Kh Lim 1715 hypertensive type 2 diabetics were randomly assigned to receive irbesartan, amlodipine or Placebo. There was a reduced risk of ESRD or doubling of serum creatinine by 20 – 23% in irbesartan compared to amlodipine or placebo (18). RENAAL trial was done on 1513 type 2 diabetic patients with nephropathy. These patients were randomly taking either losartan or placebo, in addition to other antihypertensive medications. During the trial there was a decreased risk of ESRD or serum creatinine doubling with 25 – 28% with losartan compared to placebo. In RENAAL trial the effects were also independent from the lowering of the blood pressure. [21]

Three studies reviewed by Jicheng Lv et al ARBs showed that there was no significant decrease in the risk of serum creatinine doubling or ESRD compared to placebo or no treatment. Only 3/6217 individuals that received ARBs progressed to ESRD (20). Later on, in 3 other studies under the review of Giovanni FM Strippoli et al, ARBs compared to placebo or no treatment had a reduced risk in doubling of serum creatinine
by 21 %. The same three studies, with 3251 patients, also demonstrated to reduce the risk of ESRD by 22 % in the group receiving ARB. [21]

9.12.3. Combined therapy: ACE inhibitor and ARB

Therapy by both ACE-I and ARB have been compared to monotherapy by either of those two drug groups in several studies. According to Andy Kh Lim combination therapy in earlier studies was demonstrated to be superior over monotherapy in decreasing albuminuria. This mentioned superiority occurred in both type 1 and 2 diabetes. Dual therapy was also shown to decrease the BP (mainly diastolic) more strongly compared to single therapy. [18]

Two studies were discussed by Jicheng Lv et al where difference in new onset microalbuminuria or macroalbuminuria compared dual therapy to ACE-I alone. These two studies, with 4303 patients, didn’t show clear significance between dual therapy and monotherapy, although dual therapy showed some superiority (few percentages). [20]

ONTARGET trial, another study found in the review of Andy Kh Lim, studied combined therapy of Ramipril and Telmisartan in diabetic nephropathy. During ONTARGET trial, patients didn’t show any significant changes of the incidence when looking to dialysis or doubling of serum creatinine.

Lastly, Andy Kh Lim in his article reported that combination therapy in previous studies (ONTARGET trial and NEPHRON-D study) was shown to have higher incidence of acute renal failure and hyperkalemia. Due to those mentioned adverse effects, combined therapy strategy has now been excluded for patients with diabetic nephropathy. [18]

Combined treatment of diabetic nephropathy by ACE-I and ARB was studied and compared to monotherapy by Linda F. Fried et al. The study of Linda F. Fried et al was performed between July 2008 and September 2012. During their study several aspects were studied: urinary albumin excretion, BP, changes of GFR, adverse effects etc. During randomization to one year there was a significant decline of urinary albumin-to creatinine ratio in combination therapy compared to monotherapy. Median urinary albumin-to creatinine ratio dropped from 786 to 517 and 829 to 701 respectively (P<0.001). During the study done by Linda F. Fried et al there was not much of difference in the changes of the GFR (22). The rates of acute kidney disease and hyperkalemia were higher in dual therapy in comparison to single therapy, which made the study end earlier than expected. [20]
Dual therapy has been shown to significantly reduce the BP, but also showed to reduce albuminuria according to Peter Jacobssen. [25]

**9.12.4. ACE inhibitor versus ARB**

In a meta-analysis done by Giovanni FM Strippoli et al there were no significant results in ACE-I and ARBs for progression from micro to macroalbuminuria. These results were however taken from just 1 trial studied with 41 patients. [21]

**Summary of pharmacological treatment effect on diabetic nephropathy**

<table>
<thead>
<tr>
<th>Drug (s)</th>
<th>Antiproteinuric</th>
<th>Preserve GFR</th>
<th>Diabetes type</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>++</td>
<td>++</td>
<td>Type 1 and 2</td>
</tr>
<tr>
<td>ARB</td>
<td>++</td>
<td>++</td>
<td>Type 2</td>
</tr>
<tr>
<td>ACE inhibitor plus ARB</td>
<td>+++</td>
<td>–</td>
<td>Type 1 and 2</td>
</tr>
</tbody>
</table>

Figure 4. Summarized effect of ACE-I and ARB on DN in both types of diabetes

Around 30 decades ago, Tauguma et al, reviewed by Nicolás Roberto Robles in a study showed the antiproteinuric effect of ACE-I in diabetic patients.

When comparing ACE-I and ARBs, two of the largest studies were ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study 13 and Ramipril Efficacy in Nephropathy (REIN) Study 14. There was a reduced risk in the progression to the end point in the first study mentioned above (measured to 53 % in patients with mild renal insufficient, and in patients with moderate insufficient to 46 %). The latter study mentioned previously observed a safe reduction in the decline of glomerular filtration rate, but Ramipril also showed to half the combined risk of serum creatinine doubling or ESRD, compared to other antihypertensive medications (with same level of blood pressure control) or placebo. [19]

Nicolás Roberto Robles et al performed a study on 239 type 2 diabetic patients, either assigned to ACE-I or ARBs (154 treated by ACE-I and 85 treated by ARBs). The study included an age range of 60.1±12.9, and for these patients the dosages of the drugs were adjusted to maximum tolerated dosages (except for
normotensive or hypotensive patients which received lower doses). A criteria to be included into this trial was a treatment period of at least 6 month by one of these medications. Kaplan-Meier survival analysis was used to measure survival before progressing to ESRD (GFR <15) or starting renal replacement therapy. Comparison was made at intervals after starting the treatment, first after three years and afterwards after five and seven years.

The results from Nicolas Roberto Robles et al. study demonstrated an ESRD-free survival of:

- 91.9% at three years, 81.6% at five years and 61.9% at seven years follow-up in patients who received ACE–I.
- 95.3% at three years, 82.1% at five years and 78.2% at seven years follow-up in patients treated by ARBs

In figure 5 below, Kaplan-Meier survival curves for the ACE inhibitor group and the ARB group have been demonstrated from this study.

In the same study of Nicolas Roberto Robles the absolute risk of initiating renal replacement therapy or reaching ESRD was measured. Patients treated by ACE-I had an absolute risk of 0.46, while patients receiving ARBs had a value of 0.14. ACE-I had a 3.25 times higher relative risk compared to patients treated by ARBs (95% confidence interval 0.101–0.449). [19]

Other results later on in the study was demonstrated for 135 patients (61 events) that received ACE-I and 85 received (11 events) ARBs, in a follow-up of 84 month. The comparative odds ratio for either reaching ESRD or starting renal replacement therapy was 0.227 ((95% confidence interval 0.111–0.461, p<0.001 for chi-square and likelihood ratio tests). Patient treated by ACE-I had a cohort risk ratio of 2.90 (95% confidence interval 1.640–5.128) meanwhile patients using ARBs a ratio of 0.657 (95% confidence interval 0.556–0.777).

Comparative odds ratio measured for reaching ESRD or starting renal replacement therapy at 36 month of therapy was 0.246 (95% confidence interval 0.114–0.531, p<0.001 for chi-square and likelihood ratio tests). Cohort risk of ACE inhibitors with the value of 2.768 (95% confidence interval 1.481–5.172), while ARB had a ratio of 0.682 (95% confidence interval 0.578–0.804). [19]
In a meta-analysis done by Giovanni F M Strippoli et al 49 studies with 12,067 were used to compare ACE to ARB, 7 of which compared ACE inhibitors with ARB. No differences were shown in mortality rates between ACE and ARB. The effect of renal outcomes (prevention of micro- to macroalbuminuria, remission of micro to normoalbuminuria, doubling of serum creatinine, rates of ESRD) were similar in both drug groups. [23]

In a cohort study in Taiwan, performed by Lung-Sheng Wu et al, ACE-I was compared to ARB. This study had a mean follow-up of 3.9 years during 26,809 person-years for the ACE-I group and a mean follow-up of 3.2 years during 41,292 person-years for ARB. The incidence (person-years) of developing ESRD showed to be 0.44 % and 0.63 % in ACE –I and ARB respectively. The figure below demonstrates Kaplan-Meier curves for ESRD-free for those two groups of drugs. In the graph we could visualize the lower incidence of ESRD in ACE-I compared to ARB. [24] (Figure 6)
The same study by Lung-Sheng Wu et al further added the group of patients with CKD, analyzing the effect of it on ESRD. These were for 23,353 person-years in a mean follow-up of 3.9 years for patients treated by ACE and 34,928 person-years in a mean follow-up 3.3 years for those treated by ARB. For those patients the incidence (person-years) for ACE – I and ARB were 0.30 and 0.37 % respectively, shown in the table below. The results and graphs from this study shown below showed no significant differences between the two groups. (HR 0.76; 95 % CI 0.55–1.06, P = 0.11). [24] (Figure 7)

Several studies for the last years have been comparing the occurrence of different side effects of ACE-I and ARB. The main adverse effects evaluated and compared between the two drug groups were cough, hyperkalemia, headache and impotence. According to latest studies and meta-analysis it was found that
cough occurred in a higher incidence in patients treated by ACE-I than those by ARB. In the other mentioned adverse effect, there was no significant increase in risk of occurrence in any of these groups. Also, no significant differences were found between ACE-I and ARB in the incidence of developing hyperkalemia, headache and impotence. [19, 20, 21]
10. RESEARCH METHODOLOGY

This research was a meta-analysis, comparing the results on diabetic patients that developed or showed increased in risk developing diabetic nephropathy. 25 references, 3 books and 22 articles were totally used for our comparison and analysis. Inclusion criteria was relatively broad and contained: diabetic patients (regardless type, sex, and gender). The later studies collected were focusing on outcomes based on urinary albumin, serum creatinine changes, GFR and ESRD rates.

In our results we directed the focus on four main studies (two related to the risk of smoking and two comparing ACE-I to ARB).

10.1. Initial search and collection of information
Initially the research started after building a broad, general understanding in the anatomy and physiological properties of the kidneys, related to our research topic. This information was found in the review of Ganong Medical Physiology (23rd edition) combined with a smaller part from a previous study. Material related to the objectives was thereafter collected from articles. Our search was thereafter divided into four entities: diabetes, diabetic nephropathy, the association of smoking to the disease and lastly comparison of ACE-I and ARBs. The search of these entities was relatively wide as the exclusion criteria was minimal.

321 articles were totally collected from the start of this work.

10.2. Assessment of eligibility
Later on, the selection of the search were based on: title, abstract, review, results and discussion, for which the list of articles could meet our eligible criteria. The studies published later than 2000 were excluded, with the majority of studies published last 10 years (3 studies between 2000 and 2008)

Most of the articles chosen were excluded due to: duplicates, inaccessible articles, late publicity, only related to pediatric population, studies done on non-diabetics, studies related to certain genetic mutations, comparison of other drug groups rather than ARB or ACE-I.

10.3. Inclusion criteria
Articles eligible for our meta-analysis had following criteria to meet: English language, published in the last 2 decades, with the majority of studies the last 10 years, based on humans, diabetic patients (not required to a specific type), and smokers with diabetes. Finally 23 articles and 2 books were included into our study. (Figure 8)
321 articles collected after initial search

162 articles remained for further review

71 articles remained after 2nd exclusion

159 articles excluded due inaccessibility, late publicity and duplicates

91 studies excluded after review of the abstract
(Studies related to pediatric population or certain genetic mutations)

49 studies excluded after accurate result and discussion review
(Comparison of other drug groups rather than ARB or ACE-I)

22 articles relevant for determined objectives

Figure 8. Process of article selection
11. RESULTS

11.1. The risk of smoking
For the evaluation of smoking risk, data from 2 different studies are included and compared. The first study was a case control study performed in Aleppo by Rabi et al, 2005-2009. The second study was cross-sectional study done by Hyungseon Yeom et al, 2011-2013

11.1.1. The study of Rabi et al (Aleppo)
569 diabetics were included into the study, from which 198 were diagnosed with DN (28.3 % as DN) and 371 were healthy. Women and men were equally distributed in both groups. The mean age of both group was 45.36 ± 15.95 years. The control group, healthy individuals (without CKD), had a GFR > 90 mL/min per 1.73 m² and urine ACR <0,15. Patients diagnosed with CKD, the case group, had a GFR <60 mL/min per 1.73 m² (stage 3-5 CKD). Smokers included into the study smoked at least 1 cigarette/day for at least 6 month

Primarily smokers were compared to non-smokers. Thereafter former smoker were compared to current smokers. Former smokers were those who quit smoking for >5 years ago, and current smokers that smoked for the last 5 years.

In this study, smoking (regular and current) was associated with increased risk by 2,24x to have CKD occurred by DN. Former and regular smokers increased the risk to develop CKD (regardless type) with 1,6x and 1,63x respectively. (Table 2) When considering amount/time of smoking, the risk to develop CKD increased proportional to pack-years of cigarette smoking. For those who smoked 15-30 pack-years the risk was 2,04 and for those who smoked >30 pack-years the risk further increased to 2,6 x. [12] (Figure 9)

![Figure 9. CKD risk in relation to pack-years smoked](image-url)
11.1.2. The study of Hyungseon Yeom et al (Korea)

In this cross-sectional study 629 diabetic patients, only males, were included. Patient that were included to those who had DN required to have microalbumuria or GFR <60 mL/min per 1.73 m². A large part of included patients had several risk factors like older age, longer duration of diabetes, higher HbA1c and higher systolic BP. Modifiable risk factors were adjusted and results were taken before and after adjustment. The smoker group was divided into patients who smoked only before diagnosis of diabetes and patients who ever smoked after diagnosis. 2 of the main data noted were risk to develop CKD and ACR.

The risk to develop DN increased by 1,29x (adjusted 1,23x) in those who smoked before diagnosis and 1,83x (adjusted 2,12x) times for patients who ever smoked after diagnosis. ACR was increased in both groups. The risk of progressing to microalbumuria was insignificant in the group who every smoked before diagnosis, but 1,93x for those who ever smoked after. 1,28x for those who smoked only before diagnosis and 3,6x for those who ever smoked after diagnosis to develop macroalbuminuria. [13] (Table 2)

<table>
<thead>
<tr>
<th>Risk for</th>
<th>Aleppo</th>
<th>Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>1,63</td>
<td>1,63</td>
</tr>
<tr>
<td>Progression to Microalbuminuria</td>
<td>Not measured</td>
<td>Not measured</td>
</tr>
<tr>
<td>Progression to Macroalbuminuria</td>
<td>Not measured</td>
<td>Not measured</td>
</tr>
</tbody>
</table>

Table 2. The difference between the results of smokers in Aleppo and Korea
11. Outcomes differences: ACE-I vs ARB
In the comparison of ACE-I and ARB the 2 results of studies have been collected. The first one is the DETAIL trial and the second one is a large meta-analysis by Jicheng Lv, on thousands of patients.

11.2.1 DETAIL trial

The DETAIL (Diabetics Exposed to Telmisartan And enalaprIL) study was 5 year double blind trial, review by Andy Lim Akh. The trial was performed done on 250 type 2 diabetic patients, some of who already developed DN. 120 were assigned to Telmisartan (80 mg) and 130 to Enalapril (20mg). Inclusion criteria were: patients 35-80 year, GFR>70, BP <180/95. At the start point GFR was measured for all patients, and several measurement were taken annually. Those measurements were: Serum creatinine levels and GFR, urinary albumin excretion, BP, and rates of ESRD. 82 patients (68%) of those treated with Telmisartan and 86 patients (66%) from those with Enalapril continued till the end of the trial. The reasons for quitting the trial before the end were adverse effect, non-compliance, mistrust of the trial, and other not mentioned reasons. The use of concomitant cardiovascular medications (aspirin, statins, antihypertensives) by trial patients increased during the study period.

UAE (ratio) was almost the same in the 2 drug groups at the end of the trial. The change from the baseline values were 1,03 and 0,99 Telmisartan and Enalapril respectively. (Figure 10) Regarding the GFR the annual measurements showed: -7,6, -13,2 and -16,5 at 1,2 and 3 years respectively, and was almost the same in both groups. At 4th and 5th year the GFR change was insignificant. The negative values indicate the loss of GFR. (Figure 11)

There was a small amount of patient with overt nephropathy. No individual developed a serum creatinine > 200 µmol/L and none required dialysis during the five-year study period. [18]
11.2.2. Meta-analysis by Jicheng Lv et al

To this large meta-analysis, diabetic patients of both types, were studied. Patients included for the study were had no kidney disease and normoalbuminuria. ACE-I and ARB were both compared to placebo or no treatment. Urinary albumin, GFR and progression rate to ESRD were measure at the beginning and end of treatment. In several studies comparing any of the group to placebo or no treatment other BP lowering medications were not ascertained.

At first, level of albuminuria was compared between the two groups:

- ACE – I vs placebo/no treatment: In 8 studies (11906 participant) the risk to develop new onset micro – or macroalbuminuria was reduced by 29 %.
- ARB vs placebo/no treatment: In 5 studies (7653 participant), the risk to develop new onset micro – or macroalbuminuria was reduced by 10 %. In this group a larger amount patients had CV disease, had type 2 DM rather than type 1 and had a higher baseline risk of albuminuria progression. (Figure 12)

Thereafter the comparison of GFR and ESRD progression rate were compared in ACE vs ARB:

- ACE-I vs placebo/no treatment: In 5 studies (10749 patients) there were no significant difference
- ARB vs placebo/no treatment: In 3 studies (6217 patients) there were no significant difference.
Figure 12. Change of urinary albumin in ACE-I vs ARB
12. DISCUSSION

12.1. The relation of smoking to diabetic nephropathy in diabetics
Smoking was shown to increase the risk in development and progression of diabetic nephropathy by several means. Several studies which were reviewed by Rabi Yacoub et al clearly demonstrated the impact of smoking. In their review it was reported that smoking increased the risk in developing albuminuria, thereby decreasing the period between start of diabetes and proteinuria or albuminuria. The same study further explained that smoking accelerates the progression from microalbuminuria to proteinuria, but also was shown to increase the risk of developing ESRD in diabetics. According to Chase et al albumin excretion was higher by around 2.8x in smokers compared to non-smoking individuals, meanwhile quitting smoking was shown to decrease albuminuria significantly. Supporting these facts, our results from the cross-sectional study, of Rabi et al, demonstrated increased risk in developing CKD in diabetics by 2.24x in smokers compared to the non-smoking group. In our results we also showed that the risk of developing CKD also increased in proportion to the amount of cigarette smoking [12]

Our results also included a study from Korea in which the risk of having a diabetic nephropathy was increased differently depending on the smoking behavior. Those who ever smoked after diagnosis of diabetes had a higher risk compared of those who smoked only before diagnosis, with 1,83x and 1,29x increased risk respectively. Elevated urine albumin/creatinine ratio was also increased by those that only smoked before diagnosis of diabetes, but also for those who ever smoked after the diagnosis (1,28x and 3,6x respectively). [13]

Stephan et al added that current smoker had a higher risk in developing and progression of diabetic nephropathy. Clearly by their results they showed that both current and former smoker had increased risk of microalbuminuria, but current risk with a higher RR (3.26 and 2.69 respectively). PREVEND trial was another important study reviewed by Stephan et al that demonstrated the relation of amount of cigarette smoking to urinary albumin excretion. The added amount of cigarettes/day further increased the risk for the presence of microalbuminuria. Smoking >20 cigarettes/day had a RR of 1,98 compared to <1,33 for those who smoked <20 cigarettes /d. [16]

Regardless to the type of diabetes, smoking increased GFR loss according to studies reviewed earlier. Biensenbach et al concluded that smoking increased GFR loss by 1,44x in type 1 diabetes. [13]
Temduang Chuahirun et al also stated a higher GFR decline in smokers compared to non-smoker in type 2 diabetes by twice the risk, despite the therapy by ACE-I and good control of BP. It’s worth to mention that the smoking was the only predicted, examined risk factor of DN. [15]

12.2. Outcome comparison between ACE-I and ARB
In both diabetes type 1 and type 2 ACE and ARB markedly influenced the urinary albumin, although the documented results had differences between the two drug groups. Both the drug groups showed in most reviewed studies in this meta-analysis to lower the risk of progression from micro- to macro albuminuria. Andy Kh Lim in part of his study discussed about treatment options of diabetic nephropathy. In the summary of pharmacological treatment of DN (table), we could see that ACE-I has been effective for both type 1 and 2 diabetics, and were ARB mainly been effective for type 2. (18) This choice of treatment according to the type of diabetes was also mentioned in Harrison’s, in their discussion of DN treatment. [1]

Most studies reviewed in this meta-analysis agreed on the great effectiveness of ACE-I compared to placebo or no treatment in reducing or delaying new onset albuminuria. This effectiveness could although not be seen in many studies for ARB.

In our results DETAIL trial, a study of 250 patients, showed that there was no superiority of ACE-I over ARB taking urinary albumin and GFR levels into consideration. A meta-analysis of eight studies and 11906 participants, also included in our results however demonstrate other results. ACE-I compared to placebo/no treatment reduced new onset micro- or macro albuminuria by 29%, compared to 10% reduction by ARB showed in figure 12, in our results.

In Collaborative Study Group trial, ACE-I was even showed to enable remission of nephrotic-range proteinuria. Similar benefits in reduction or delaying urinary albumin could not be demonstrated for ARB compared to placebo/no treatment in our results or most of our reviewed studies. However two studies showed a great benefit of using ARB in delaying or preventing the progression of DN. According Giovanni FM Strippoli et al the progression from micro to macroalbuminuria was reduced by 55% in individuals using ARB. [21] Nicolas Roberto Robles also demonstrated a reduction in reducing the risk of initiating renal replacement therapy or reaching ESRD by both groups, although ARB was favored. [19]

Comparing the two drug groups regarding serum creatinine changes and the rate of ESRD, different studies came to different results and conclusions. Many studies concluded that there was no difference between the
drug groups in the changes of serum creatinine and ESRD rate, while other studies favored one of them. In our results neither of the groups was superior to placebo or no treatment decreasing the reduction of GFR. In Collaborative Study Group trial, Captopril reduced the serum creatinine doubling by 48%. [18] REIN trial demonstrated both a safe reduction in GFR decline by Ramipril. In addition the drug also halved the risk of serum creatinine doubling or ESRD in Ramipril treated patients compared to other hypertensives or placebo. [19] A study done in Taiwan clearly favored the use of ACE-I over ARB in diabetic patients. The incidence in developing ESRD were 0.44% in patients treated by ACE-I, compared to 0.63% in patients treated by ARB. Later on in the same study of Lung-Sheng Wu et al, in the study done in Taiwan, they added the group of patients with CKD. The rate of ESRD occurrence were 0.30% in patients with CKD treated by ACE-I. Patients with CKD treated by ARB had an occurrence rate of 0.37%. [24] Different numbers were shown by the study of Nicolas Roberto Robles, another study comparing ACE-I and ARB, which favored ARB over ACE-I. The study included 239 type 2 diabetics who were followed up at intervals of three, five and seven years. Measuring the ESRD-free survival rate, ARB was superior to ARB. [19] Summarizing the reviewed studies comparing either ACE or ARB to placebo or no treatment, ACE had a superiority in delaying or reducing onset risk of micro or macroalbuminuria in diabetic patients. ACE might be more effective compared to ARB, considering the results of previous studies. Certain studies although reported heterogeneity when comparing ARB to placebo or no treatment. Several patients in those studies included for ARB contra placebo faced heterogeneity due to patients with previous cardiovascular disease or other risk factors.

Comparing ACE-I against ARB in the serum creatinine or GFR changes and the rate of ESRD demonstrated different results. Many of those studies mentioned that there could be bias possibly reflecting these results. The different trials reviewed had different age groups, uncertain effects of other BP lowering agents and patients with different concomitant risk factors.

12. 3. The difference between dual therapy and monotherapy in diabetic patient
Combined therapy by ACE and ARB had obvious benefits in the occurrence or progression of urinary albumin. Andy Kh Lim meant that dual therapy had a superiority over monotherapy in decreasing albuminuria in both type 1 and type 2 diabetes. BP (mainly diastolic) was lowered in a greater amount in dual therapy combined to single therapy. [18] A study done by Linda F.Fried et al in their study dual treatment had a significant decline of urinary albumin-to-creatinine ratio compared to monotherapy. [19] 2 other studies with 4303 patients, discussed by Jicheng LV et al, contradicted the benefits of dual therapy
discussed in other studies. These 2 studies showed that dual therapy didn’t have significant superiority (or possible only by few percentages) over monotherapy in reducing new onset micro – or macroalbuminuria. [20]

The reason of benefits in dual blockade shown in several studies could not be surely explained. Theories explained that it might be the extra step in blocking RAS system or by its effect of reducing the blood pressure.

ONTARGET trial mentioned that the incidence of dialysis or doubling of serum creatinine was not changed in dual treatment compared to monotherapy.

Despite its possible effectiveness, dual therapy has been excluded for patients with diabetic nephropathy, due to higher incidence of acute renal failure and hyperkalemia. [18]

It’s known worldwide and proved by mentioned studies earlier that ARB replaces ACE-I when patients suffer from cough. [19, 20, 21]
13. CONCLUSION

1) Smoking is a major, independent risk factor in development and progression of diabetic nephropathy and CKD. It increases the risk of developing albuminuria but also increases the risk of progression from one stage of albuminuria to another.

2) In both type 1 and 2 diabetes patients, GFR loss was increased in smokers compared to non-smokes.

3) Both the smoking behavior and amount played an important role in increasing the risk of progression.

4) Overall ACE-I showed a superiority over ARB in delaying or reducing the new onset albuminuria. Some of the studies included into our review although faced heterogeneity (other BP agents were not ascertained and larger groups of patients taking ARB had cardiovascular and other risk factors)

5) Different data were demonstrated regarding serum creatinine, GFR changes and ESRD. One of the largest meta-analysis included in our results could not show efficacy in neither of the drug group compared to placebo or no treatment.

6) Dual therapy showed superiority to monotherapy, but nowadays it is rarely used due to higher incidence of adverse effects (higher incidence of acute renal failure and hyperkalemia)

Further investigations need to either exclude or equally distribute other BP affecting medications between the trial groups. We suggest otherwise studies in future to display the association between the effect of BP reduction and treatment by either of the discussed drug group on albuminuria and creatinine clearance more clearly. According to a previous study it’s not always possible to prove a relation between albuminuria and renal function. GFR will not necessarily be normalized by simply prevention of albuminuria. Cardiovascular and other risk factors that possibly could bias the results should, if possible, be adjusted in order to get more conclusive results. In case of unalterable risk factors, later trials need to illustrate the influence of possible risk factors on urinary albumin and kidney function.

There are no clear superiority clearly shown, although ACE-I perhaps could be more effective in earlier stages. In some cases the ARB can replace ACE-I due to less side effects shown.
14. REFERENCES


2. Abrahamson DR. *Role of the podocyte (and glomerular endothelium) in building the GBM*. PubMed – NCBI [Internet]. 2012; 07


4. Vecihi Batuman, MD, FASN et al. *Diabetic nephropathy*. Medscape [Internet]. 2017; 5
   Medscape [Internet]. Updated 2017;12
   Available from: https://emedicine.medscape.com/article/238946-overview#a34

   Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527883/


8. M R Moosa, I van der Walt; S Naicker; A M Meyers. *Important causes of chronic kidney disease in South Africa*. South African Medical Journal [Internet]. 2015; 03
   Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2474786/
10. Ki-Chul Sung, MD, PhD, Seungho Ryu, MD, PhD, Jong-Young Lee, MD, PhD, Sung Ho Lee, MD, PhD, EunSun Cheong, MD, Young-Youl Hyun, MD, PhD,Kyu-Beck Lee, MD, PhD, Hyang Kim, MD, PhD, and Christopher D. Byrne, MBBCh, PhD. Urine Albumin/Creatinine Ratio Below 30 mg/g is a Predictor of Incident Hypertension and Cardiovascular Mortality. PubMed – NCBI [Internet]. 2016;09
   Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5079007/
   Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3004836/
   Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4829370/
15. Temduang Chuahirun (MD), Donald E.Wesson (MD). Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. PubMed – NCBI [Internet]. 2002;02
   Available from:


Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4818874/