

The Effect of Chronic Cigarette Smoking on some Kidney Function Markers

ABSTRACT

Background / Aim: One of the organs that are negatively impacted by smoking is the kidney. The purpose of this study is to compare the mean serum levels of urea and creatinine, microalbumin, albumin-creatinine ratio, and estimated glomerular filtration rate of smokers to non-smokers and their implications to ascertain the impact of chronic cigarette smoking on some kidney function markers.

Methodology: This investigation was conducted in and around Anambra State's Newi Metropolis. Two hundred participants, ranging in age from 20 to 40, were chosen at random and involved in the study. They were divided into two groups: the control group, which consisted of 100 healthy males, and the smoker's group, which consisted of 100 male smokers who smoked at least seven sticks a day. All subjects had blood drawn, and spectrophotometric techniques were used to determine the levels of microalbumin, uric acid, serum urea, and creatinine. Each individual filled out questionnaires on their personal information, medical history, and drug use. The participant was permitted to observe 10 minutes of sat resting to allow fluid shifts to equilibrate, reducing variability in a pre-analytical variable

Results: Analysis of the data revealed that, as compared to the control patients, smokers had significantly higher mean levels of urea, creatinine, urine albumin (malb), albumin-creatinine ratio, and estimated glomerular filtration rate ($p < 0.05$). When compared to the control group, the serum urea and creatinine levels in the smoking group were considerably higher ($p > 0.05$).

Conclusion: Smokers experience negative effects on their renal function. Renal function was negatively impacted in the smoker's group, they experience elevated serum creatinine and urea level. Since there is a decline in the filtration rate in the glomerular, an increase was observed in the urea and creatinine level as a result of the decline. Nicotine usage does have several systemic effects mostly in connection with creatinine and urea in renal illness.

Keywords: Albuminuria, Creatinine, (GFR) Glomerular Filtration Rate, Kidney, Tobacco Use, Urea

INTRODUCTION

Smoke from tobacco products, including tobacco, contains a variety of dangerous chemicals. One of these compounds that can be obtained through both active and passive smoking is nicotine. Smoking's addictive potential and physiological consequences are principally mediated by nicotine, the main tobacco alkaloid. Repeated smoking is encouraged by stressful professions, which also support addictive habits.

For many years, tobacco (*Nicotiana Tobacum*) has been farmed in Africa. Smokeless tobacco consumption is currently on the rise in the United States of America (USA) [2] and is extremely common in the Far East, Middle East, and Europe [1]. But in Nigeria, potash is added as an ingredient to the powdered form known as "tobacco snuff." It can either be applied topically or inhaled (sniffed) through the nose. There are two types of tobacco: chewing tobacco and tobacco snuff. Tobacco can be consumed in a variety of ways.

The most prevalent form of tobacco usage is cigarette smoking. If the current pattern holds by 2030, smoking will result in the yearly death toll exceeding 9 million. According to the Minister of Health, Prof. Isaac Adewole, smoking is a growing public health issue, particularly in emerging nations like Nigeria. In recent years, it has been clear that smoking is linked to excessive morbidity and mortality in several illnesses, most notably lung and cardiovascular diseases[3]. In addition, the kidney is a key target organ for smoking-related harm, and 4.5 million people in Nigeria smoke 20 billion sticks of tobacco annually. The World Health Organization (WHO) reported in May 2017 that tobacco kills more than 7 million people a year, 6 million of whom die directly from using it and the remaining 200,000 through being exposed to smoking[4]. Our nation's leaders ought to be concerned.

Catecholamine circulation is stimulated by increased sympathetic nervous system activity. Vasoconstriction results from this in the vascular system. Vascular resistance rises by 11% in the Renovascular bed. This results in a 15% decrease in the glomerular filtration rate and an 18% decrease in the filtration fraction [5]. Less is known about the long-term impact of smoking on renal health. There is proof that chronic smokers have lower renal plasma flow, which is associated with a little increase in endothelin. Functioning problems are brought on by endothelin through vaso-constriction.

Only a small number of studies examined the effects of smoking on kidney function, and they did so only in a few specific population groups, including those with diabetes mellitus, primary kidney diseases like polycystic kidney disease, glomerulonephritis, and lupus nephritis, or, more recently, those with atherosclerotic renal artery stenosis [6].

Furthermore, K. Yamagata's [7] epidemiologic study from 2007 demonstrated a link between smoking and a higher risk of chronic renal disease development and kidney failure in people with diabetes and high blood pressure.

In patients with type 2 diabetes, researchers recently found a dose- and time-dependent relationship between smoking and an increase in the prevalence of chronic kidney disease (CKD) and the urinary albumin-creatinine ratio [8].

The incidence and progression of CKD may be influenced by smoking, regardless of the underlying disease, according to a recent meta-analysis [9] based on 15 prospective cohorts and including more than 65,000 incident CKD patients. However, interestingly, there was no correlation between smoking and proteinuria.

When tobacco is burned, radioactive substances are released into the air, which smokers breathe into their lungs. This could be another important risk factor for lung cancer in smokers [10]. The hazardous and cancer-causing substances in cigar smoke are largely the same as those in cigarette smoke, albeit some of them are present to varying degrees. Cigar tobacco has high levels of several nitrogen compounds as a result of the aging (fermentation) process used to create cigars (nitrates and nitrites). These chemicals release numerous tobacco-specific nitrosamines (TSNAs), some of the most potent cancer-causing agents known when the fermented cigar tobacco is smoked [11]. The tobacco doesn't burn as completely in a cigar because the wrapper is less porous than a cigarette wrapper. Higher levels of tar, nitrogen oxides, ammonia, carbon monoxide, and other toxic compounds are produced as a result.

However, there is currently limited knowledge regarding how smoking affects glomerular filtration rate, non-protein nitrogen (NPN) metabolites (creatinine and urea), uric acid, microalbumin, albumin-creatinine ratio, and overall kidney function. As they are used to assess renal function integrity, renal function tests are crucial components in the laboratory diagnosis and prognosis of renal dysfunction as well as in the monitoring of therapy response in medicine, particularly in renal pathology.

Urea is synthesized in the liver and then delivered by the plasma to the kidney, where the glomerulus easily separates it from the plasma. [12] Although up to 40% of the urea in the glomerulus is reabsorbed by passive diffusion as the filtrate travels through the renal tubules, the majority of urea in the glomerulus is expelled in the urine. The amount that is reabsorbed is influenced by hydration level and urine flow rate. Urea is eliminated by the kidneys in greater than 90% of cases, with the remaining 10% passing through the GI tract and skin.

In muscles, creatine phosphate is broken down into creatinine. Utilizing two enzymatic processes, arginine, glycine, and methionine are converted into creatine in the kidneys, liver, and pancreas [13]. It is subsequently transferred to various tissues, including muscle and the brain, where it is changed into the highly energetic molecule phosphocreatine.

The urine protein albumin is now known to be the kidney and the heart's initial indicator of arterial injury. The occurrence of albuminuria has been known for more than 200 years, and Richard Bright's ground-breaking discoveries in 1827 are what first linked it to kidney illness. The protein the body utilizes for growth and repair is called albumin. However, when the

kidneys aren't functioning properly, albumin leaks into the urine (a medical disease known as albuminuria) [14]. A significant protein called albumin is often found in the blood, but when the kidneys are working correctly, there is essentially no albumin in the urine.

The majority of the time, an albumin-to-creatinine ratio (ACR) is determined after tests for albumin and creatinine are performed on a urine sample that was randomly obtained (not timed). To give a more precise indication of how much albumin is being released into the urine, this is done. The amount of creatinine in the urine, which is a consequence of muscle metabolism and a reliable indicator of urine concentration, is typically delivered into the body at a consistent rate. When measuring albumin in a random urine sample, this feature of creatinine enables its measurement to be used to adjust urine concentration.

A minor amount of albumin in the urine may be a sign of renal disease at an early stage [15]. Urine microalbumin or microalbuminuria are terms used to describe a trace amount of albumin in the urine. The term "albuminuria," which refers to any elevation of albumin in the urine, is gradually replacing "microalbuminuria."

Blood's liquid component, plasma, is made up of a variety of proteins, including albumin. Plasma protein preservation is one of the kidneys' many jobs to prevent waste products and plasma proteins from being discharged together when urine is made. Normal protein absorption into urine is prevented by two mechanisms:

The kidney's glomeruli are specialized structures made up of loops of specialized capillaries that filter blood and enable small particles to pass through toward the urine while acting as a barrier to keep the majority of big plasma proteins inside the blood vessels.

Smaller proteins that do get through the glomeruli are almost totally reabsorbed by tubes (tubules) that have numerous sections that collect the fluid and molecules.

Most frequently, kidney injury to either the glomeruli or tubules results in protein in the urine (proteinuria). Protein can leak into the urine at increasing levels due to glomeruli inflammation and/or scarring. Protein absorption can be impeded by tubule damage[16]. One of the first proteins to be found in urine with kidney injury is albumin. People who persistently have trace levels of albumin in their urine (albuminuria) are more likely to eventually develop cardiovascular disease and progressive kidney failure.

The National Renal Foundation advises the estimation of GFR for use in the diagnosis, care, and prevention of chronic kidney disease. It is regarded as the top general indication of renal health [17]. Numerous people with impaired renal function cannot be identified by serum creatinine alone. As an illustration, senior citizens may lose 50% of their kidney function before their serum creatinine level exceeds the normal limit. The National Kidney Foundation

This study compares the mean serum levels and evaluates the impact of chronic cigarette smoking on a few kidney function measures. The purpose of this analysis was to assess the association between cigarette smoking and albuminuria in an adult male population sample with normal basal kidney function due to the lack of information regarding the effect of cigarette smoking, in the general population, on the risk to develop subclinical kidney damage, such as the increase of albuminuria.

METHOD AND MATERIALS

Study design

Between the ages of 20 and 40, this study included 100 male cigarette smokers (test) and 100 male non-smokers (control). Smokers and non-smokers were divided into two groups. The smokers in this category have been routinely smoking for at least 4 years, averaging at least 7 cigarettes each day. The study analyzed the average serum levels of urea and creatinine in smokers and non-smokers to look for any potential links between smoking and renal function markers, as well as any consequences. For this study, 200 adult respondents in the Anambra state metropolises of Okofia and Nnewi, ranging in age from 20 to 40, were chosen at random.

For all subjects, a screening questionnaire containing questions about health history, drug use, and personal information was created. For this project, materials including a tourniquet, a 5ml syringe, heparinized blood containers, plain plastic containers, cotton wool, swabs, a spectrophotometer, a refrigerator, and a centrifuge will be used. 40g/l sodium dodecyl sulfate (sodium lauryl sulfate), pH 12.8, phosphate buffer Diacetyl monoxime, 60 percent v/v Acetic acid, reagent for picric acid, and reagent for urea acid.

Criteria for inclusion/exclusion

100 people (smokers) who have been smoking for at least five years and consistently consume at least 7 cigarettes a day and 100 people (non-smokers) who have never touched a cigarette. Exclusion criteria for this study included those with a history of salicylates, thiophenylpyrazolidine, atophan, probenecid, or allopurinol over-the-counter drugs, as well as those with diabetes, renal, sickle cell, or malignant disease, medical therapy, or vitamin supplement use currently and smokeless tobacco patients. Each participant was permitted to observe 10 minutes of sat resting to allow fluid shifts to equilibrate, reducing variability in a pre-analytical variable. Without letting the tourniquet remain on for longer than a minute, blood was drawn from the median cubital vein using a clean venipuncture technique to get roughly 5ml of blood. To obtain the serum, blood was diluted into test tubes, allowed to coagulate, and then

spun at 3000 rpm for five minutes. A separate, labeled test tube was used to separate the supernatant (based on serial numbers on the sample).

Analytical Statistics

Using SPSS, the statistical analysis will be carried out (Statistical Package for the Social Sciences). P values of <0.05 and <0.01 will be considered significant values. The spearman's correlation coefficient will be used to assess the relationship between the parameters and the severity of the condition.

Sample Size

The sample size will be calculated using the method described by Charan and Biswas, (2013);

$$N = \frac{Z^2 p \cdot q}{d^2}$$

$$d^2$$

Where:

N= Desired number of samples when the population of the facility is limited

Z = The standard normal variance where the confidence level is 1.96 at 95%

p = prevalence rate of cigarette smoking in Anambra Nigeria is 3.1% (Ezekwesili et al, 2016)

$$q = 1 - p$$

d = 5% i.e degree of precision as desired by the researcher.

Applying the method,

$$N = \frac{Z^2 \cdot P \cdot (1-P)}{D^2}$$

$$D^2$$

$$N = \frac{1.96^2 \times 0.031 \times 1 - 0.031}{0.05^2}$$

0.0025²

N=200 ± 10%

Results

The variation of the Mean values of serum creatinine, urea, uric acid, MALB, ACR, and eGFR in smokers and non-smokers in **table 1**

There was a significant difference in the mean creatinine, urea, and microalbumin ($p < 0.05$). the mean values of creatinine, urea, and microalbumin were higher in the smoker's group than their respective mean values in the non-smoker's group.

There was a significant difference in microalbumin was higher in smokers compared to non-smokers (control).

The mean value of estimated glomerular filtration rate (eGFR) ($p < 0.05$) in smokers was lower compared to non-smokers (control).

There was no significant difference in the mean value of uric acid ($p > 0.05$). The mean value of uric acid in smokers was higher compared to that of non-smokers.

In table 2 The correlation of the average amount of cigarette sticks per day with creatinine, urea, uric acid, albumin-creatinine ratio, and estimated glomerular filtration rate and microalbumin in smokers.

There was a strong positive correlation between the levels of urea, creatinine, and uric acid in smokers in comparison with the average amount of cigarette sticks consumed daily.

There was a strong positive correlation between the levels of the albumin-creatinine ratio (ACR) and microalbumin (Malb) of the smokers when compared with the average amount of cigarette sticks consumed daily.

There was a strong negative correlation between the estimated glomerular filtration rate (eGFR) in comparison to the average sticks of cigarettes smoked daily.

Table 1 shows the mean levels of serum creatinine, urea, uric acid, malb, ACR, and eGFR in

Parameters	r	p-value
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chronic smokers and non-smokers. (mean±SD).

Parameters	Non-smokers	Smokers	Mann-Whitney (u)	t-value	p-value
Creatinine(μmol/l)	74.80±24.713	132.33±68.10	-6.023	7.9	0.000
Urea(mmol/l)	4.45±1.64	6.50±2.97	-2.996	6.02	0.003
Uric acid	339.81±135.22	377.80±174.30	-0.760	1.7	0.447
Malb (mg/l)	47.19±25.38	59.91±46.80	-0.429	2.4	0.001
Acr (mg/mmol)	7.94±6.62	11.15±7.13	-2.420	3.4	0.016
eGFR(mL/min)	133.23±30.63	81.50±27.56	-6.092	12.6	0.000

Table 2 shows the Correlation of the average amount of cigarette sticks per day with creatinine, urea, uric acid albumin-creatinine ratio and estimated glomerular filtration rate and microalbumin in smokers.

Smokers	Av. Sticks vs Creatinine	0.103	0.528
	Av. Sticks vs Urea	0.044	0.798
	Av. Sticks vs Uric acid	0.125	0.442
	Av. Sticks vs ACR	0.415	0.008
	Av. Sticks vs eGFR	-0.102	0.533
	Av.sticks vs Malb	0.390	0.013

Keywords:

ACR = Albumin-Creatinine ratio

eGFR = Estimated Glomerular Filtration Rate

MALB = Microalbumin

SD = Standard Deviation

DISCUSSIONS

One of the organs that are negatively impacted by smoking is the kidney. This study demonstrates how smoking affects renal function as measured by serum urea and creatinine levels. It demonstrates that smokers had significantly higher serum levels of urea and creatinine than non-smokers at (p0.05) and (p0.05), respectively. These results are consistent with those of Yuka [18] and El Sayed et al. (2013). Additionally, they could be brought on by the influence of smoking, which raises renovascular resistance and causes a considerable decline in renal plasma blood, filtration fraction, and glomerular filtration rate (GFR) [19]. The decline in GFR will

cause the distal tubular flow rate to decline, which will enhance urea reabsorption [20]. Serum creatinine was much greater in smokers than in non-smokers, according to Halimi's study from 1998 [21], which demonstrated that smoking increases creatinine levels. Additionally, this research partially supports a study by Pittilo et al. [22] that found smokers had higher creatinine clearance (ml/min/1.73m²) than nonsmokers. [23] The study also found that smokers had considerably higher mean urine albumin levels than non-smokers, which is consistent with research was done by R K. Gupta et al. in 2014. Notably, microalbuminuria was more common in smokers.

Smoking was found to be a separate factor in the cardiac outcome preventive evaluation research to determine microalbuminuria [24]. One of the primary mechanisms through which smoking results in albuminuria and decreased renal function is through advanced glycation end products (AGEPs). AGEPs, which are cross-linking moieties, are created when reducing sugars interact with the amino groups of plasma proteins, lipids, and nucleic acids. The aqueous extracts of tobacco and cigarette smoke contain glycotoxins, highly reactive glycation products that can rapidly trigger AGEP formation on proteins in vitro and in vivo, as Cerami et al.,1997 has recently demonstrated [25]. The systemic and renal vasculature are expected to be affected similarly by the AGEPs produced by the reaction of glycotoxins from cigarette smoke with serum and tissue proteins as was previously mentioned. Another mechanism based on the pathophysiological effect of smoking-induced kidney damage is insulin resistance. Numerous researches have found a connection between smoking and insulin resistance in non-diabetic patients [26]. Albuminuria and impairments in renal function have both been linked to insulin resistance. Both procedures lead to endothelial dysfunction by disrupting the balance between the substances the endothelium produces to contract and relax. Smokers have been reported to have greater plasma levels of endothelin 14 than non-smokers, and there is indirect evidence that smoking interferes with endothelin, prostacyclin, or nitric oxide release when prompted [27].

Damage to the vascular system is one of the many harmful health effects of cigarette smoking. Smoking has been linked to arteriosclerosis, which includes the renal arteries. Additionally, it's linked to kidney and other organ thickenings of tiny arteries as well as arteriolar hyalinosis. Vascular injury and renal vasoconstriction may be caused by some processes [28-30]. Catecholamines, arginine, vasopressin, and endothelin-1 are among the vasoconstrictors whose plasma levels are increased by nicotine [19,31]. [22] Smoke from cigarettes harms endothelium cells, and nicotine promotes the growth of smooth muscle cells. [30] Another study linked sympathetic nervous system activation to renovascular resistance. A prior study found that smokers had greater serum levels of cadmium and lead than non-smokers, which suggested that the Lead-linked glomerular dysfunction they experienced may have been the result of more recent exposure to high levels of lead. Seven cigarettes smoked daily result in an estimated 3.6–6.0 Lg of Cd being inhaled, which is cumulatively nephrotoxic.

The nephrotoxicity of cadmium [32] causes changes in proximal tubular function, characterized by increased excretion of beta 2-microglobulin and causing the classic tubular proteinuria, as well as glomerular dysfunction, which is indicated by increased excretion of high molecular weight proteins, increased levels of beta 2-microglobulin and creatinine in plasma, and leading to glomerular type proteinuria. These findings imply that chemicals found in cigarettes can have a serious impact on renal tubule PH and alter the glomerular filtration rate.

Conclusion

In this work, an effort has been made to identify the biochemical alterations that occur when smoking and reflect renal function. The elevated serum urea and creatinine levels in the smoker group show that renal function is negatively impacted. The considerable decline in the glomerular filtration rate is what is responsible for the increase in creatinine and urea (GFR). There is evidence that nicotine usage has a variety of systemic consequences, especially in light of the relationship between urea and creatinine in renal illness. The deleterious effects of cigarette smoking on these metabolites appear to be confirmed by the higher mean serum levels of urea and creatinine in active smokers. This analysis also demonstrates that smoking was independently related to the development of greater albuminuria levels over time in a group of male adults without microalbuminuria and with normal kidney function.

Ethical Approval

Before the study started, the ethics committee for the Faculty of Health Science and Technology granted its clearance for the research.

Consent

Before the study, the subjects' informed consent has been collected and preserved by the author(s).

REFERENCES

1. Bates C, Fagerstrom K, Jarvis MJ, Kunze M, McNeil A, Ramstrom L. European Union policy on smokeless tobacco. A statement in favor of evidence-based regulation for public health. *Tobacco Control*. 2003; 12, 360–367
2. Changrani J, Gany F, Paan, Gutkha in the United States. An emerging threat. *J. Immig. Health*. 2005; 7:103–108.

3. Saha SP, Bhalla DK, Wayne TF Jr, Gairola C. Cigarette smoke and adverse health effects. An overview of research trends and future needs. *Int J Angiol.* 2007;16(3):77-83.
4. World Health Organization WHO. World No Tobacco Day. Beating tobacco for health, prosperity, the environment and national development. 2017; Geneva Switzerland
5. Muhammad AMK, Jackson T, Said K, Muhammad AUK, Rabeea A, Arslan RU. Cigarette Smoking and Its Hazards in Kidney Transplantation. *Advances in Medicine.* 2017; 11 pages
6. Drummond CA, Brewster PS, He W, Ren K, Xie Y, Tuttle KR, Haller ST, Jamerson K, Dworkin LD, Cutlip DE, Murphy TP, D'Agostino RB Sr, Henrich WL, Tian J, Shapiro JJ, Cooper CJ. Cigarette smoking and cardio-renal events in patients with atherosclerotic renal artery stenosis. *PLoS One.* 2017;12(3):e01
7. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M, Koyama A. Risk factors for chronic kidney disease in a community-based population. a 10-year follow-up study. *Kidney Int.* 2007; **71**(2), 159–166
8. Ohkuma T. Dose- and time-dependent association of smoking and its cessation with glycemic control and insulin resistance in male patients with type 2 diabetes mellitus. The Fukuoka Diabetes Registry. *PloS one* **10**, 2015
9. Jia X, Lin W, Zhiheng M, Liping Z, Ying W, Yachan G, Liqun H, Xiao S. Cigarette smoking and chronic kidney disease in the general population. a systematic review and meta-analysis of prospective cohort studies. *Nephrology Dialysis Transplantation.* Volume 32, 2017; 475–487,
10. Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tobacco Control.* 2003;12(4):424–30
11. Yalcin E, de la Monte S. Tobacco nitrosamines as culprits in disease. mechanisms reviewed. *J Physiol Biochem.* 2016 ;72(1):107-20
12. Raforth R, Onstad G R J. Urea synthesis after oral protein ingestion in man. *Journal of Clinical Investigation.* 1975; **56**:1170–1274
13. Kassirer J P. Clinical evaluation of kidney function. glomerular function. *New England Journal of Medicine.* 1971; **285**:355–899
14. Glassock RJ. Prevention of Microalbuminuria in Type 2 Diabetes. Millimeters or Milligrams. *J Am Soc Nephrol.* 2006;17:3276–3278
15. Amitava D, Amer W. Renal Function Tests. *Clinical Chemistry, Immunology, and Laboratory Quality Control.* 2014; 197-212

16. Anne D. Proteinuria Clinical Biochemistry. Metabolic and Clinical Aspects (Third Edition) Churchill Livingstone. 2014; Pages 152-167
17. Ogobuiro I, Tuma F. Physiology Renal. In: StatPearls [Internet]. TreasureIsland (FL) StatPearls Publishing. 2022
28. El SS, M, Mahmoud HS, Nabo MMH . Medical and Scientific Bases of Wet Cupping Therapy (Al- hijamah). in Light of Modern Medicine and Prophetic medicine. *International Integrative Medicine*. 2013; **2**(3):89-98
19. Ritz E, Benck U, Franek E, Keller C, Seyfarth M, Clorius J. Effects of smoking on renal hemodynamics in healthy volunteers and patients with glomerular disease. *Journal of the American Society Nephrology*.1998; **9**(10).1798-1804.
20. Joann L, Robert WS. Blood Urea Nitrogen A Marker for Adverse Effects of Loop Diuretics. *Journal of the American College of Cardiology*. 2011; **58**:58-164
21. Halimi JM, Mimran A. Renal effects of smoking. potential mechanisms and perspectives. *Nephrology Dialysis Transplantation*. 2000; **15**:938-998
22. Pittilo R M, Bull HA, Gulati S. Nicotine and cigarette smoking.Effects on the ultrastructure of aortic endothelium. *International Journal of Experimental Pathology*. 1990; **71**:573–586
23. Gupta RK, Gupta R, Maheshwari VD, Mawliya M. Impact of smoking on microalbuminuria and urinary albumin creatinine ratio in non-diabetic normotensive smokers. *Indian J Nephrol*. 2014; **24**(2):92-6
24. Gerstein, Hertz C. Prevalence and determinants of microalbuminuria in high-risk diabetic and nondiabetic patients in the heart outcomes prevention evaluation study.*Diabetes care* **23**. 2000: B35.
25. Cerami, Carla. Tobacco smoke is a source of toxic reactive glycation products. *Proceedings of the National Academy of Sciences* **94**.25 (1997); 13915-13920
26. Artese A, Stamford BA, Moffatt RJ. Cigarette Smoking: An Accessory to the Development of Insulin Resistance. *Am J Lifestyle Med*. 2017; **13**(6):602-605
27. Messner B, Bernhard D. Smoking and cardiovascular disease. mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol*. 2014; **34**(3):509-15
28. Sharrett A R, Ding J, Criqui MH. Smoking, diabetes, and blood cholesterol differ in their associations with subclinical atherosclerosis. the Multiethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2006; **186**:441- 447.

29. Appel R G, Bleyer A J, Reavis S. Renovascular disease in older patients beginning renal replacement therapy. *Kidney International*. 1995; **48**: 171–176
30. Black HR, Zeevi GR, Silten RM, Smith GJW. Effect of heavy cigarette smoking on renal and myocardial arterioles. *Nephron*. 1983, **34**:173–179
31. Gambaro G, Verlato F, Budakovic A. Renal impairment in chronic cigarette smokers. *Journal of the American Society Nephrology*. 1998; **9**:562–567
32. Roszczenko A, Galazyn SM, Brzoska M, M, Moniuszko J, Zwierz J, K. Chosen parameters of the kidney function in smokers in relation to the exposure to cadmium. *Przegląd Lekarski*. 2004; **61**:348-350