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*Professional paper*

# CORRELATION BETWEEN OXIDATIVE STRESS AND DIABETES

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**Abstract**

The pancreas is a very important gland of the human body, which produces insulin and glucagon, two important hormones that maintain proper blood sugar levels. Diabetes mellitus on the other hand is a chronic medical condition characterized by high levels of glucose (sugar) in the blood due to problems with insulin production, insulin action, or both. Oxidative stress (OS) is a physiological condition that occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these harmful molecules or repair the resulting damage. Reactive oxygen species are reactive molecules that contain oxygen, such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals. These molecules are produced as natural byproducts of various cellular processes, but excessive accumulation of ROS can lead to cellular damage and contribute to various diseases.

The purpose of this paper is to highlight the cases of diabetes that are related to oxidative stress in the regions of North Macedonia as a growing phenomenon year after year. Also, the purpose of the research lies in the deep understanding of this connection which can open the doors to innovative treatments that directly affect the molecular mechanisms of oxidative stress, offering hope for a more effective and personalized approach in the management and treatment of diabetes.

As material for this study, were used the statistical data provided by the Institute of Public Health-Skopje. For diabetes statistics, the patient's blood as an analytical sample, and it was measured with a glucometer device which works on the principle of amperometry, where the maximum current obtained during an electrochemical reaction is taken as an indicator of the concentration of the analysis. Oxidative stress is a complex phenomenon and no method gives a real insight into its exact level. The part of measuring oxidative stress was done based on the quantitative method through patient questionnaires, with anamnesis (medical history of the patient) and with the patient survey where we used topics, questions, subjective complaints about their symptoms, and professional research about the field of stress as a phenomenon. The study is included in the regions of the Republic of North Macedonia and it covers 2020.

In recent years there have been encouraging steps in understanding and studying the pathogenesis of diabetes related to oxidative stress. The epicenter of much research has been and is finding the key cause for recognizing the deep connection between oxidative stress and diabetes. This research aims to shed light on the need for therapeutic strategies aimed at reducing oxidative stress and preventing its damage to the body.

*Keywords:* Pancreas, diabetes mellitus, oxidative stress (OS), reactive oxygen species (ROS).

## 1. Introduction

Publication The Human body is continuously exposed to different types of agents that result in the production of reactive species called free radicals (ROS/RNS) which by the transfer of their free unpaired electron causes the oxidation of cellular machinery. To encounter the deleterious effects of such species, the body has endogenous antioxidant systems or it obtains exogenous antioxidants from a diet that neutralizes such species and keeps the homeostasis of the body. Any imbalance between the RS and antioxidants leads to a condition known as “oxidative stress” that results in the development of pathological conditions among which one is diabetes. Most of the studies reveal the inference of oxidative stress in diabetes pathogenesis by the alteration in enzymatic systems, lipid peroxidation, impaired Glutathione metabolism, and decreased Vitamin C levels. Lipids, proteins, DNA damage, Glutathione, catalane, and superoxide dismutase are various biomarkers of oxidative stress in diabetes mellitus. Oxidative

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stress-induced complications of diabetes may include stroke, neuropathy, retinopathy, and nephropathy (UllahAsmat*et al.*, 2015).

WHO (World Health Organization, 2023. https://www.who.int/news-room/fact-sheets/detail/diabetes) states that Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood glucose. Hyperglycaemia, also called raised blood glucose or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

Type 1 diabetes (previously known as insulin-dependent, juvenile, or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin.

Type 2 diabetes affects how your body uses sugar (glucose) for energy. It stops the body from using insulin properly, leading to high blood sugar levels if not treated.

Gestational diabetes is hyperglycemia with blood glucose values above normal but below that diagnostic of diabetes. Gestational diabetes occurs during pregnancy.

Women with gestational diabetes are at an increased risk of complications during pregnancy and delivery. These women and possibly their children are also at increased risk of type 2 diabetes in the future.

Early diagnosis can be accomplished through relatively inexpensive testing of blood glucose.

One of the most important ways to treat diabetes is to keep a healthy lifestyle.

Some people with type 2 diabetes will need to take medicines to help manage their blood sugar levels. These can include insulin injections or other drugs. Some examples include: metformin, sulfonylureas, and sodium-glucose co-transporters type 2 (SGLT-2) inhibitors (World Health Organization, 2023).

Diabetes mellitus is a group of metabolic disorders that are characterized by elevated levels of glucose in the blood (hyperglycemia) and insufficiency in the production or action of insulin produced by the pancreas inside the body (Maritim*et al.*,2003).

Free radicals (e.g., superoxide, nitric oxide, and hydroxyl radicals) and other reactive species (e.g., hydrogen peroxide, peroxynitrite, and hypochlorous acid) are produced in the body, primarily as a result of aerobic metabolism. Antioxidants (e.g., glutathione, arginine, citrulline, taurine, creatine, selenium, zinc, vitamin E, vitamin C, vitamin A, and tea polyphenols) and antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidases) exert synergistic actions in scavenging free radicals. There has been growing evidence over the past three decades showing that malnutrition (e.g., dietary deficiencies of protein, selenium, and zinc) or excess of certain nutrients (e.g., iron and vitamin C) gives rise to the oxidation of bio-molecules and cell injury. A large body of the literature supports the notion that dietary antioxidants are useful radioprotectors and play an important role in preventing many human diseases (e.g., cancer, atherosclerosis, stroke, rheumatoid arthritis, neurodegeneration, and diabetes) (Yon-Zhon Fang *et al.*, 2002). It is believed that oxidative stress plays an important role in the development of vascular complications in diabetes particularly type 2 diabetes (Pham-Huy*et al.*, 2008). ROS level elevation in diabetes may be due to a decrease in the destruction or/an increase in the production by catalase (CAT—enzymatic/non-enzymatic), superoxide dismutase (SOD), and glutathione peroxidase (GSH–Px) antioxidants. The variation in the levels of these enzymes makes the tissues susceptible to oxidative stress leading to the development of diabetic complications (Lipinski, 2001). According to epidemiological studies, diabetic mortalities can be explained notably by an increase in vascular diseases other than hyperglycemia (Pham-Huy*et al.*, 2008).

In diabetes mellitus, the main sources of oxidative stress are mitochondria. During oxidative metabolism in mitochondria, a component of the utilized oxygen is reduced to water, and the remaining oxygen is transformed to oxygen free radical (O•) which is an important ROS that is converted to another RS such as ONOO-, OH, and H2O2 (Moussa, 2008). Insulin signaling is modulated by ROS/RNS in two ways. On one side, in response to insulin, the ROS/RNS are produced to exert their full physiological function and on the other side, the ROS and RNS have negative regulation on insulin signaling, interpreting them to develop insulin resistance which is a risk factor for diabetes type 2 (Erejuwa, 2012). Many pieces of evidence from experiments have given a link between diabetes and oxidative stress by measuring various biomarkers including DNA damage biomarkers and lipid peroxidation products. It is believed that in the onset and progression of late diabetic complications, free radicals have got a major role due to their ability to damage lipids, proteins, and DNA (Ayepola*et al.,* 2014). A variety of pathological conditions are induced by oxidative stress such as Rheumatoid arthritis, Diabetes mellitus, and cancer (El Faramawy and Rizk, 2011). Free radical and oxidative stress-induced complications from DM include coronary artery disease, Neuropathy, nephropathy, retinopathy (Phillips et al., 2004), and stroke (Asfandiyarova*et al.*,2007).

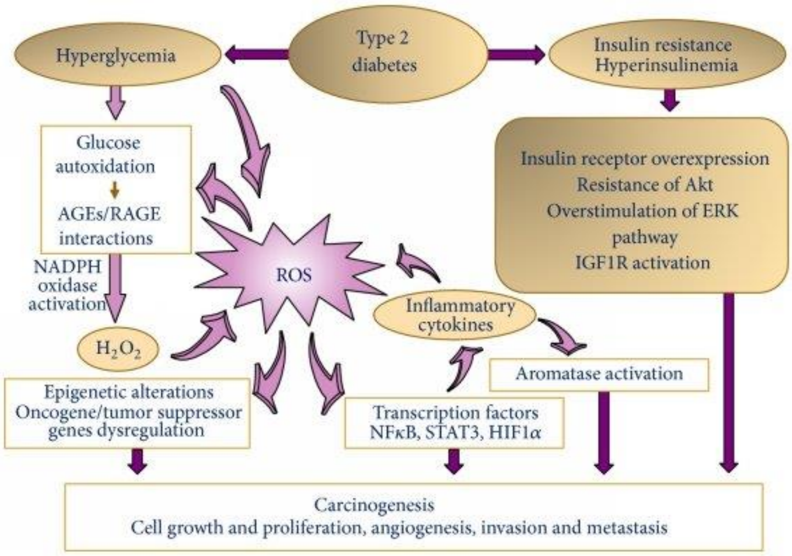



**Figure 1.** Correlation between oxidative stress pathways and diabetes mellitus

## 2. Materials and Methods

As material for this study, were used the statistical data provided by the Institute of Public Health-Skopje. The study is included in the regions of the Republic of North Macedonia and it covers 2020.

For diabetes statistics, was taken the patient's blood as an analytical sample and it was measured with a glucometer device. A glucometer, also known as a blood glucose meter, is a medical device used to measure the concentration of glucose in the blood. It is a key component in managing diabetes. A glucometer works with test strips, lancet, and the meter itself. Where each one of them has their role. The test strips contain chemicals that react with glucose in the blood. They are usually disposable and single-use. The lancet is a small needle used to prick the skin to obtain a blood sample and the meter is a device that reads the test strip and displays the glucose level. How does all of this combine?

Well, first we need preparation, a blood sample then happens the chemical reaction and the measurement. First, we insert the test strip into the glucometer. This strip contains an enzyme, typically glucose oxidase or glucose dehydrogenase, that reacts with glucose, then we used a lancet to prick the side of the patient's fingertip to obtain a drop of blood. Then the blood drop is placed on the designated area of the test strip. Capillary action pulls the blood into the reaction zone of the strip. After all this the enzyme on the test strip reacts with the glucose in the blood sample, producing a small electrical current. This is an electrochemical reaction where the glucose oxidase or dehydrogenase converts the glucose to gluconolactone, generating electrons in the process. The meter's microprocessor converts the electrical signal to a glucose concentration reading using an algorithm, which is then displayed on the screen.

As for the SO measurement part we used a combination of anamnesis, structured questionnaires, subjective complaints, and professional research to provide a comprehensive approach to understanding the patient's health in the context of stress. This method allows healthcare professionals to identify key areas of concern, monitor changes over time, and develop targeted interventions to improve patient outcomes.

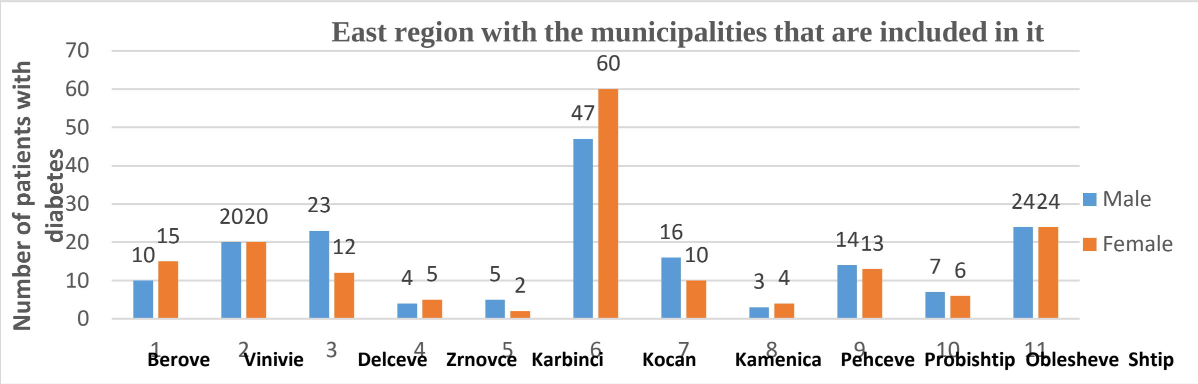
Here's a detailed breakdown of how the methods we used in the study were effectively exploited.

Anamnesis involves collecting a comprehensive medical history from the patient, which includes: personal information, medical history, family history, social history, and psychological history. Personal Information: age, gender, occupation, lifestyle habits, etc. Medical History: previous illnesses, surgeries, chronic conditions, medications, allergies, etc. Family History: genetic predispositions to certain conditions, hereditary diseases, etc. Social History: living conditions, social support systems, stressors in daily life, etc. Psychological History: previous mental health issues, psychological stressors, and coping mechanisms. All of this information helped us to find the significance between patients with diabetes and oxidative stress.

We also used patient surveys which can include structured questionnaires to assess various aspects of the patient's health, symptoms, and stress levels. These can be divided into several sections: demographic information (basic information such as age, gender, occupation, etc.), symptom checklist a detailed list of symptoms the patient is experiencing, their frequency, and severity. Subjective complaints are open-ended questions where patients describe their symptoms and how these symptoms affect their daily lives. Stress assessment includes specific questions targeting stress levels, sources of stress, and their impact on physical and mental health.

Diabetes can be diagnosed by demonstrating increased concentrations of glucose in venous plasma or increased hemoglobin A1c (HbA1c) in the blood. Glycemic control is monitored by people with diabetes measuring their blood glucose with meters and/or with continuous interstitial glucose monitoring (CGM) devices and also by laboratory analysis of HbA1c. The potential roles of noninvasive glucose monitoring, genetic testing, and measurement of ketones, autoantibodies, urine albumin, insulin, proinsulin, and C-peptide are addressed (David B. Sacks et al., 2023).

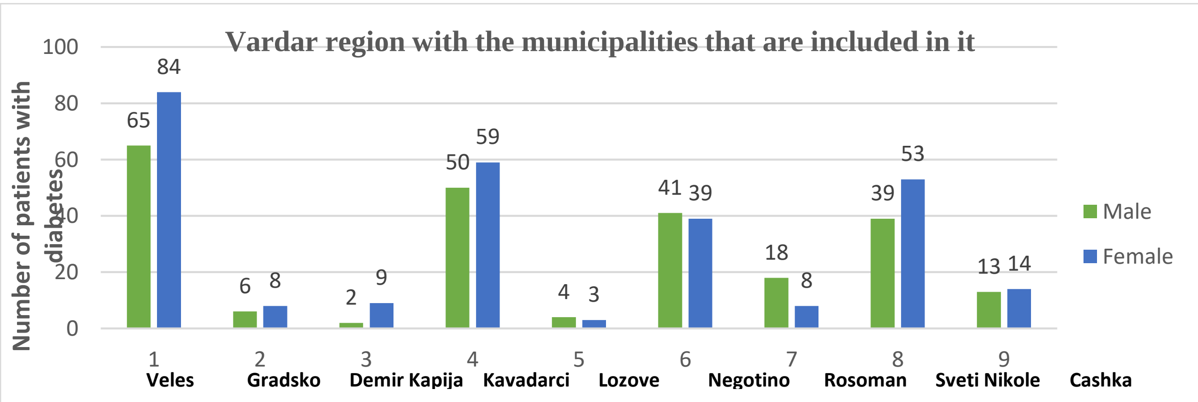
Oxidative stress is a historical concept from the time when all diseases were considered as being caused by too much free radical production or too little elimination; it was not supposed to be measured but "cured" by antioxidants. Several techniques can be used (available online: https://www.cellbiolabs.com/oxidative-cellular-stress (accessed on 17 June 2022) depending on the sample type (cells, tissues, blood, urine, food samples). Most of the tests measure the damage that radicals or excess oxidants have caused, such as DNA/RNA damage (8-Hydroxyguanosine (8-OHG), 8-Hydroxydeoxyguanosine (8-OHdG), Abasic (AP) sites, BPDE DNA Adduct, Double-strand DNA breaks, and Comet Assay (general DNA damage)). Other techniques analyze the product of lipid damage as a result of radical or oxidant impact (lipid peroxidation 4-hydroxynonenal, 8-isoprostane, malondialdehyde (MDA), and TBARS). Additionally, protein modifications have been used, such as oxidation/nitration, protein carbonyl content (PCC) 3-nitrotyrosine, advanced glycation end products (AGE), advanced oxidation protein products (AOPP), protein adducts, methylglyoxal adducts, protein radicals, and s-glutathione adducts (Jiankang Liu et al., 2022).




Despite the accumulated knowledge on SO in many serious pathophysiological processes, measurement of ROS is still difficult. Electron spin resonance has been recognized as the most powerful technique for the detection of ROS in the form of free radicals. However, ROS are short-lived and do not accumulate to high enough levels to be measured (Fumaki Ito et al., 2019).

## 3. Results and Discussion

In this study, we have explored the link between diabetes and oxidative stress, focusing on how these two phenomena interrelate and influence each other.
To collect the necessary data for our study on the correlation between diabetes and oxidative stress, we collaborated with the Institute of Public Health in Skopje. This institution has provided us with access to a database that includes information on diabetic patients, including clinical and biochemical parameters. After collecting these data, we systematically analyzed and categorized them to identify markers of oxidative stress and to assess the level of diabetes in each patient. Next, we used statistical and graphics programs to present the data in various graphs, which clearly illustrate the relationship between blood glucose levels and indicators of oxidative stress. Our results show a strong positive association, suggesting that the management of oxidative stress may be an important approach in the treatment and prevention of diabetes complications.

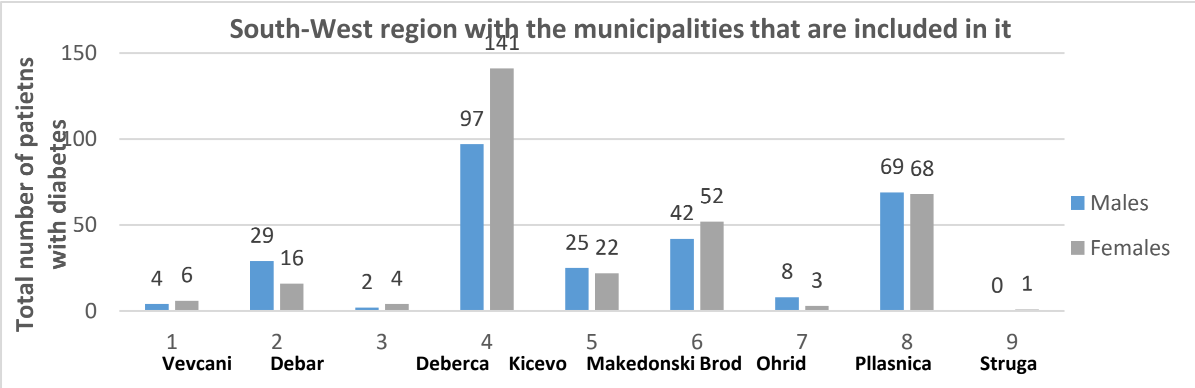



**Graphic 1**. General data of the work sample for diabetes, in the region of Vardar with the municipalities that are included in it.

Where we can clearly see that the city of Veles, Kavadarci, Lozova with Rosomani are the places most attacked by the factors that bring the significant connection between diabetes and oxidative stress. We also see a clear picture where the female gender is more affected by diabetes than the male gender.

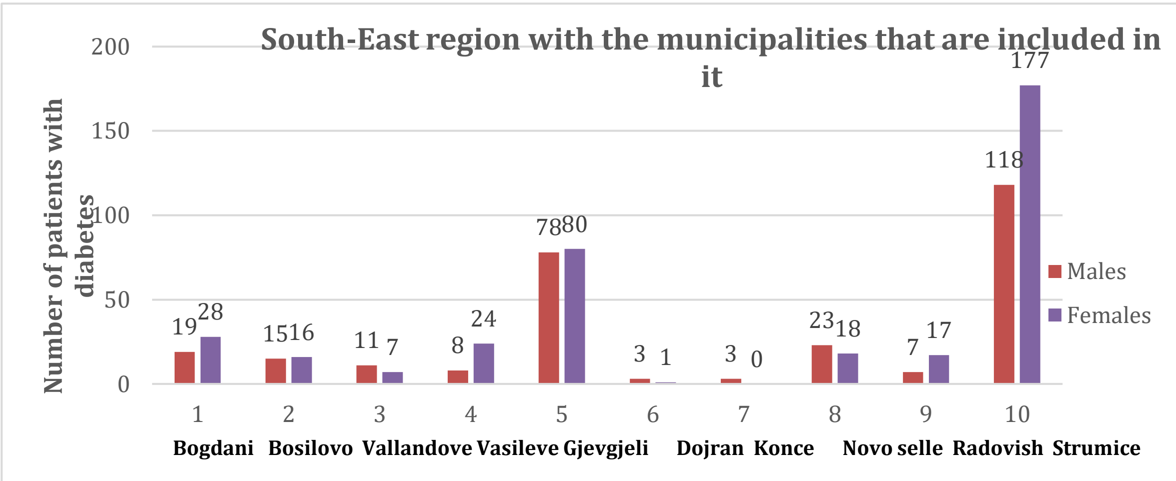
**Graphic 2.** General data of the work sample for diabetes, in the East region with the municipalities that are included in it.

The characteristic of the Eastern region is that the municipality of Kocani has a higher number of patients affected by diabetes than the rest of the regions with municipalities per district.



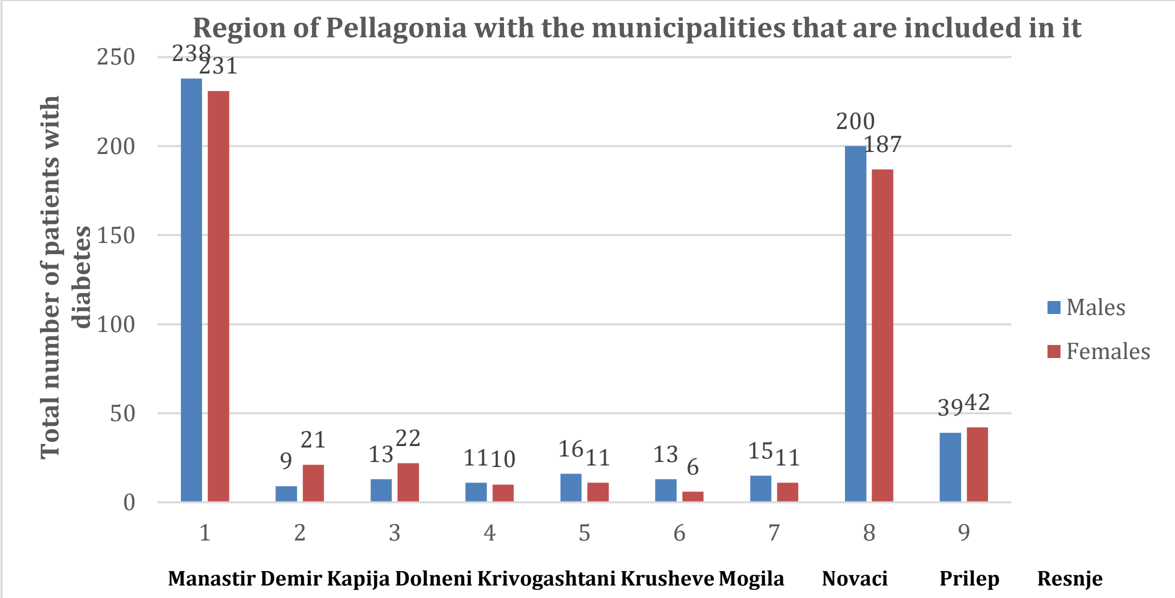

**Graphic 3.** General data of the work sample for diabetes, in the South-West region with the municipalities that are included in it.

In the graphic, we can easily see that Kicevo and Struga are the municipalities with the highest levels of diabetes compared to other municipalities in the South West region.



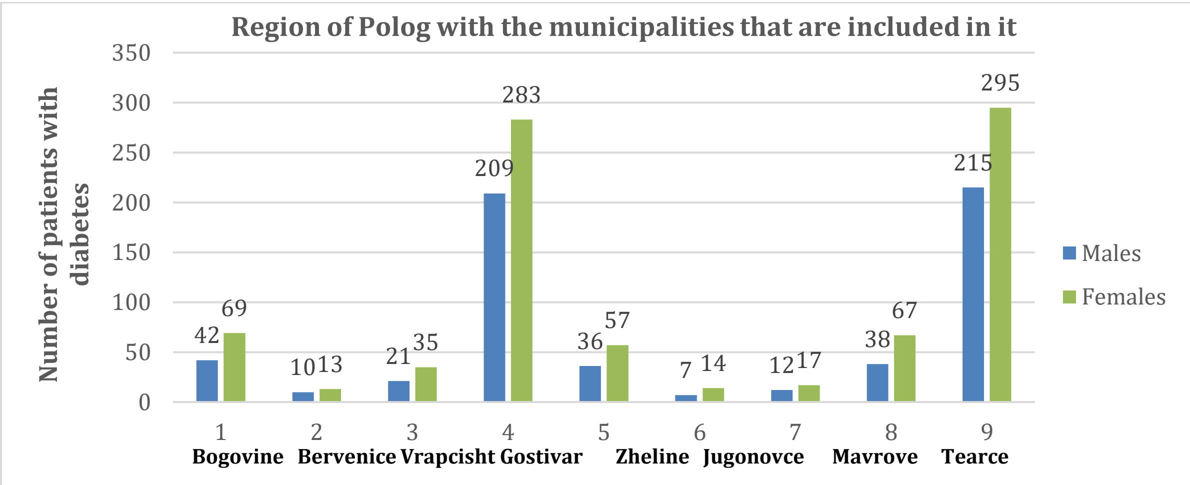

**Graphic 4**. General data of the work sample for diabetes, in the South-East region with the municipalities that are included in it.

Characteristic for the south-east region is that only the municipality of Strumica with its villages has reached the maximum number of patients with diabetes, where it is found that one of the connecting or significant factors is oxidative stress, and of course, the most affected is the female gender.



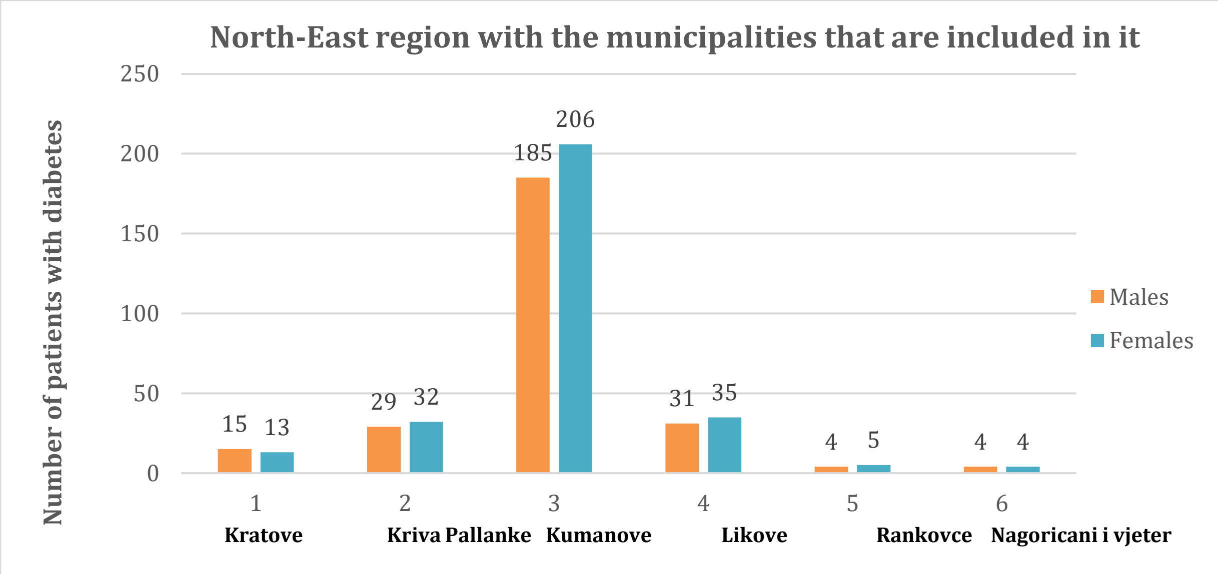

**Graphic 5**. General data of the work sample for diabetes, in the region of Pelagonia with the municipalities that are included in it.

Likewise, in the region of Pelagonia, we have two maximums of two municipalities. The municipality of Manastir with 238 men and 231 women with diabetes and the municipality of Prilep with 200 men and 187 women with diabetes. The characteristic part of the Pelagonia region is that the male gender in these municipalities is more affected by diabetes compared to other municipalities where the female gender is more affected by diabetes.



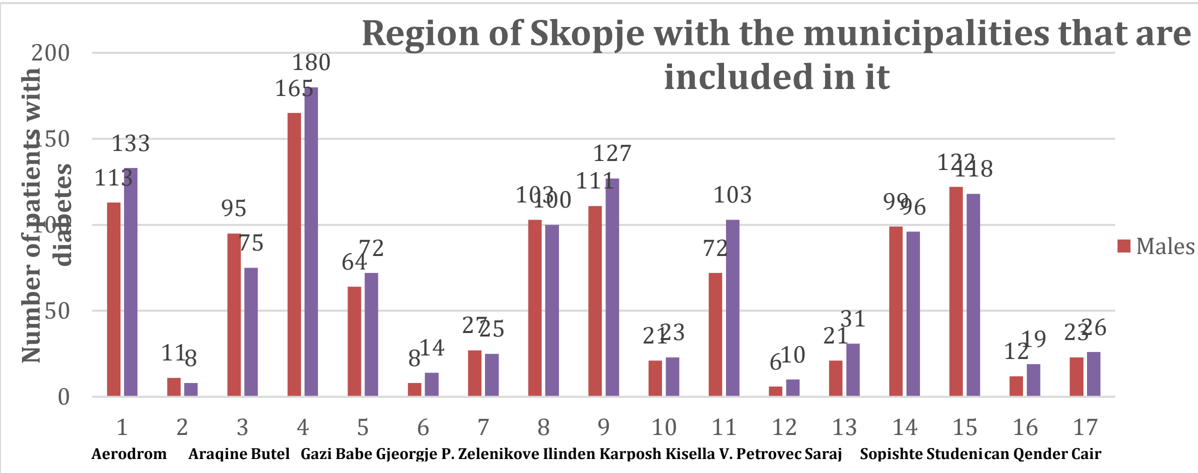

**Graphic 6.** General data of the work sample for diabetes, in the region of Polog with the municipalities that are included in it.

The region of Polog has the municipality of Gostivar with the highest number of diabetics, and the region of Tetova also has an even higher number of diabetics than the region of Gostivar.




**Graphic 7.** General data of the work sample for diabetes, in the North-East region with the municipalities that are included in it.

The North-East part has the municipality of Kumanovo most affected by diabetes, where the female gender reaches 206 people with diabetes and the male gender reaches 185 people with diabetes.




**Graphic 8.** General data of the work sample for diabetes, in the region of Skopje with the municipalities that are included in it.

Of all the regions of the Republic of North Macedonia, the region of Skopje is the most affected by the number of people with diabetes. Where almost all municipalities with surrounding villages are in an alarming state. Most of the municipalities of Skopje exceed 100 patients per municipality from only one gender, whereas from both genders there are around 200 patients affected by diabetes.

We can see here that both genders are close to each other with the number of patients with diabetes, it is not that one gender dominates the other. As the capital of RMV, this region has people with a lot of work time daily, and with that also comes daily stress, chaotic life, etc., which leads to the formation of chronic oxidative stress and then to the disease of diabetes itself.

## 4. Conclusions

From the analysis, comparison, and discussion of the data we can come to the following conclusion:

Numerous studies have shown that oxidative stress contributes to the progression of diabetes, significantly impacting insulin function and increasing the risk of complications!

In conclusion from our study, the correlation between diabetes and oxidative stress in North Macedonia underscores a significant public health concern, with notable regional and gender disparities. Our findings highlight that Skopje, the capital city, bears the highest burden of diabetes cases. This elevated prevalence can be attributed to several factors, including higher urban pollution levels, lifestyle factors such as diet and physical inactivity, and possibly greater access to diagnostic facilities leading to more reported cases. In contrast, the Northeast region exhibits a comparatively lower incidence of diabetes, potentially influenced by differences in environmental factors, dietary habits, and lower levels of industrial pollution.

Moreover, the data reveals that females in North Macedonia are disproportionately affected by diabetes. This gender disparity may stem from a combination of biological, social, and economic factors. Women may experience higher levels of oxidative stress due to hormonal fluctuations, particularly during pregnancy and menopause, which can exacerbate the risk of developing diabetes. Additionally, socio-economic factors such as access to healthcare, educational disparities, and differing health behaviors between men and women could contribute to this trend.

The contrasting scenarios between regions and the pronounced impact on females emphasize the need for targeted public health strategies to address oxidative stress and manage diabetes more effectively across the country. Tailored interventions focusing on reducing environmental pollutants, promoting healthier lifestyles, and improving healthcare access, especially for women and urban populations like those in Skopje, could play a pivotal role in mitigating the overall diabetes burden in North Macedonia.

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