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Severe Complications of Diabetic Foot Syndrome (Ulcer, Gangrene, Amputation) Are Associated with Chronic Kidney Disease

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Annotation: In this article, the authors presented the results of a review of the literature on one of the terrible complications of type 2 diabetes - diabetic foot syndrome in the stage of severe complications (ulcer, gangrene, amputation) associated with chronic kidney disease. This topic, despite its relevance, is still poorly understood.
As a result of the analysis of the literature, the authors come to the conclusion that after the start of renal replacement therapy in patients on hemodialysis, there is an increase in the incidence of the neuro-ischemic form of the diabetic foot syndrome. Along with this, the progression of chronic obliterating diseases of the arteries of the lower extremities during the observation period was noted only among diabetic patients on hemodialysis. Therefore, it is necessary to find ways for early prevention of these complications, early diagnosis and treatment.
Keywords: diabetic foot syndrome, diabetic patients, complications, CKD.

I. RELEVANCE AND EPIDEMIOLOGY OF DIABETIC FOOT SYNDROME IN PATIENTS WITH TYPE 2 DIABETES AND CKD

Complications of diabetic foot are considered to be a serious consequence of type 2 diabetes mellitus (T2DM), which poses a serious medical and economic threat. Identifying the extent of the problem and risk factors will enable health care providers to develop more effective prevention programs.

Complications of diabetic foot contribute to both mortality and morbidity among diabetics, resulting in significant physical, physiological, and financial burdens for patients and society as a whole. It is estimated that 24.4% of total healthcare costs among diabetics are due to foot complications [1], and the total cost of treating diabetic foot complications approaches US$11 billion [2] and US$456 million in the UK [3].].

The risk of ulceration and amputation in diabetic patients increases two to four times with increasing age and duration of diabetes, regardless of the type of diabetes [4]. It has also been proven by many longitudinal epidemiological studies that among patients with diabetes, the lifetime risk of foot ulcers is about 25% [5, 6], which is two-thirds of all non-traumatic amputations [7].

Foot ulcers are a preventable condition where simple interventions can reduce amputations by up to 70% with programs that can reduce risk factors [8]. Understanding the role of risk factors contributing to this condition will allow health care providers to develop more effective prevention programs that can lead to an improved quality of life for patients and therefore a reduced economic burden for both the patient and the healthcare system.

Disease registries are now considered a reliable source for monitoring chronic diseases such as diabetes and their complications. Countries such as Denmark, Sweden, Singapore, Malaysia, Saudi Arabia, and Thailand have adopted diabetes registries to monitor this disease [9–14]. In this study, performed in 2019, the Saudi National Diabetes Registry (SNDR), being one of the largest registries diabetes was used to study the prevalence of foot ulcers, gangrene and amputation and their risk factors among Saudi patients with type 1 and type 2 diabetes aged 25 years and older. SNDR is a specially designed electronic web-based data system that includes demographic data and clinical and biochemical parameters associated with diabetes. The design and development of an Internet-based SNDR has already been explained in a previously published paper [15].

A cross-sectional sample of 65,534 anonymous Saudi diabetics was recruited from the onset of SNDR in 2000 to December 2012. In this hospital-based observational study, a cohort of 62,681 patients with diabetes aged ≥25 years was selected to study foot complications and related them diseases. risk factors. 2071 (3.3%) diabetics were found to have a current or history of diabetic foot ulcer, gangrene, or diabetic lower limb amputation.

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The prevalence of diabetic foot complications in the Saudi Arabian population from this large database was found to be in the range of what is reported internationally. Diabetic foot ulcers account for more than 50% of the total number of diabetic foot cases. The presence of peripheral neuropathy and PVD is considered the most significant risk factor for all types of diabetic foot complications. This study confirmed the importance of previously known risk factors for diabetic foot complications and also demonstrated the importance of diabetic retinopathy as a significant independent risk factor to be considered during screening for foot problems in diabetic patients. [15].

II. RISK FACTORS FOR THE DEVELOPMENT OF DIABETIC FOOT SYNDROME IN PATIENTS WITH TYPE 2 DIABETES AND CKD. THE ROLE OF INDICATORS OF INFLAMMATION

A multicenter study performed in Spain and published in 2021 found an association of necrosis, serum albumin, ESR values, and neutrophil to lymphocyte ratio (SNL) with severe DFS. The presence of these predictors of severity in cases of moderate infections was significantly associated with higher amputation and recurrence rates, longer duration of antibiotic treatment, and longer hospital stay. DFS can be classified as mild, moderate, severe without systemic inflammatory response syndrome (SIRS), and severe. [18].

Recently, a lot of research is associated with various kinds of biomarkers. Diabetic foot ulcer (DFS) is one of the main complications of diabetes, and about 1% of people with diabetes have to resort to lower limb amputation. With a better understanding of the pathological basis of JDS, a number of biomarkers such as atrial natriuretic peptides, galectin-3 and cardiac troponins for diabetic cardiomyopathy, cystatin C for diabetic nephropathy, and C-reactive protein for infection and procalcitonin may help in early and non-invasive diagnosis. especially when the clinical signs are misleading. However, the predictive role of new biomarkers in primary prevention requires additional research taking into account gender, age, and multiple complications in UC. [16].

Thus, according to a multicenter study performed in Italy, procalcitonin (PCT) can be considered as a marker of a strong acute inflammatory response that reflects global deregulation, even in patients without sepsis (i.e., patients with moderate diabetic foot infection). Recent studies have shown that increased PCT is not solely due to infection, but there is a significant relationship between PCT and organ dysfunction and tissue damage, as described after cardiac surgery in patients with acute myocardial ischemia. [19]. According to a review of the literature, this is the first study that, in 2018, evaluated the role of PCT as an outcome marker in hospital patients with ischemic-infected DF.

Chinese authors have recently shown that neutrophil extracellular traps or NET-specific markers were significantly higher in diabetic foot ulcer (DNS) patients than in non-DNS diabetic patients or healthy controls, and were found to be positively correlated with assessment of the severity of diabetic ulcer - STDS and assessment of wound, ischemia and infection of the foot (RIIS). Elastase levels in ulcer tissue are significantly increased in wounds with infections and delayed healing. Higher levels of NET release were observed after stimulation of plasma or platelets from ulcer-associated vessels than from non-ulcer vessels in patients with DD. [17].

Citrullinated histone 3 (citH3) has been identified as a risk factor for impaired wound healing and amputation. Patients with the highest quartile of citH3 levels showed significantly lower rates of recovery and higher rates of amputation than those with lower three quartiles. NET-specific markers have been negatively correlated with wound healing in patients with UC, and citH3 is a potential marker. This study showed that markers specific for NETs can predict worsening of wound healing in patients with ND. It has also been found that the microenvironment around a foot ulcer causes neutrophils to release NETs, which may contribute to impaired wound healing. Thus, targeting NETs may attenuate impaired wound healing and lead to reduced amputation rates. [20].

III. FEATURES OF PROGRESSIVE ARTERIAL DISEASE IN PATIENTS WITH TYPE 2 DIABETES WITH TERMINAL CKD ON DIALYSIS

The low life expectancy of patients with diabetic nephropathy with end-stage renal disease (ESRD) on dialysis is primarily due to the high incidence of other serious complications of diabetes. One of the complications that determine the high risk of disability and mortality in diabetic patients with ESRD on dialysis is diabetic foot syndrome (DFS).

According to foreign authors [22-25], in patients with DM with the onset of ESRD (uremia), the risk of DFS increases by more than five times.

With the onset of RRT, the incidence of DFS increases significantly [26-28]. At the same time, DFS not only significantly reduces the quality of life of patients, reduces the chances of a successful kidney transplantation, but also creates a real threat of limb amputation and a high risk of mortality.

There are no data on the prevalence of DFS in patients on renal replacement therapy (RRT) in Russia. Despite the fact that every year the number of diabetic patients with ESRD, who need and receive dialysis therapy, increases every year, in our country the problem of damage to the lower extremities in patients with type 2 diabetes with ESRD has not been practically studied. It should be noted that in the foreign literature there are single works that consider this issue. According to R. Frykberg, the problem of DFS in patients with type 2 diabetes on dialysis is currently not only poorly understood, but also clearly underestimated [29].

Publications of a number of foreign researchers convincingly show that patients with type 2 DM with ESRD on RRT are at high risk of DFS and amputations of the lower extremities [30-33]. Nevertheless, according to the authors, it remains not entirely clear what pathogenetic mechanisms lead to the progression of lesions of the lower extremities, an increase in the incidence of DFS in this group of patients. According to a multicenter study performed in Poland and published in 2014, the concentrations of vascular endothelial growth factor VEGF-A and its receptors 1 and 2 in patients with well-controlled type 2 diabetes are comparable to those in healthy people, which may indicate that proper control of glucose levels delays the occurrence of vascular complications. The negative correlation between VEGFR2 and HDL-cholesterol levels and the positive correlation between VEGF-A, VEGFR2 and triglyceride levels suggest that lipid disorders occurring in diabetes may be involved in the modulation of angiogenesis. [21].

Russian author Bublik E.A. in 2008 showed in her work that the progression of chronic obliterating diseases of the arteries of the lower extremities during the observation period was noted only among patients with type 2 diabetes on hemodialysis. During the hemodialysis procedure, there is a decrease in systolic blood pressure, both in the arteries of the shoulder, and in the arteries of the legs and first toes, which can lead to a deterioration in the blood supply to the lower extremities and contribute to an increase in the risk of neuro-ischemic form of the diabetic foot syndrome. [34].

IV. MODERN POSSIBILITIES FOR THE PREVENTION AND TREATMENT OF DFS IN PATIENTS WITH END-STAGE CKD ON DIALYSIS

Back in 2009, Gunter Wolf noted that little is known about the potential association between kidney function and the development of DFS in patients with preterminal kidney disease. A retrospective cohort study was conducted at a single tertiary university center serving a large number of patients with type 1 and type 2 diabetes. All patients with type 1 and type 2 diabetes from 1989 to 2007 were analyzed, in whom all studies were performed, including albuminuria and serum creatinine. A total of 899 patients with type 1 DM and 4007 individuals with type 2 DM were examined. This observational study found a strong association between the degree of renal impairment and disease-free survival. Data show that patients with DFS are more likely to undergo amputation; thus, patients with diabetes and renal insufficiency should be advised to be regularly screened for the presence of DFS [36].

In 2008, a Czech author. Jirkovská A. noted in her study that they emphasize the need for closer collaboration not only between diabetologists, primary care physicians and nephrologists, but also with educated diabetic patients. When referring to a nephrologist, many patients do not turn on time, often too late. The most important educational information for patients is to adhere to a diet and maintain adequate control of blood pressure and type 2 DM through self-monitoring [35].

V. CONCLUSION

As a result of the analysis of the literature, we came to the conclusion that after the start of renal replacement therapy in patients on hemodialysis, there is an increase in the incidence of neuro-ischemic form of diabetic foot syndrome. Along with this, the progression of chronic obliterating diseases of the arteries of the lower extremities during the observation period was noted only among diabetic patients on hemodialysis. Therefore, it is necessary to find ways for early prevention of these complications, early diagnosis and treatment.

The data of the performed literature review led to the conclusion that this direction is very relevant. At the same time, there are no randomized placebo-controlled trials in patients with type 2 diabetes, subjected to a thorough study of the pathogenesis of the progression of two competing severe complications of the disease - DFS and CKD.

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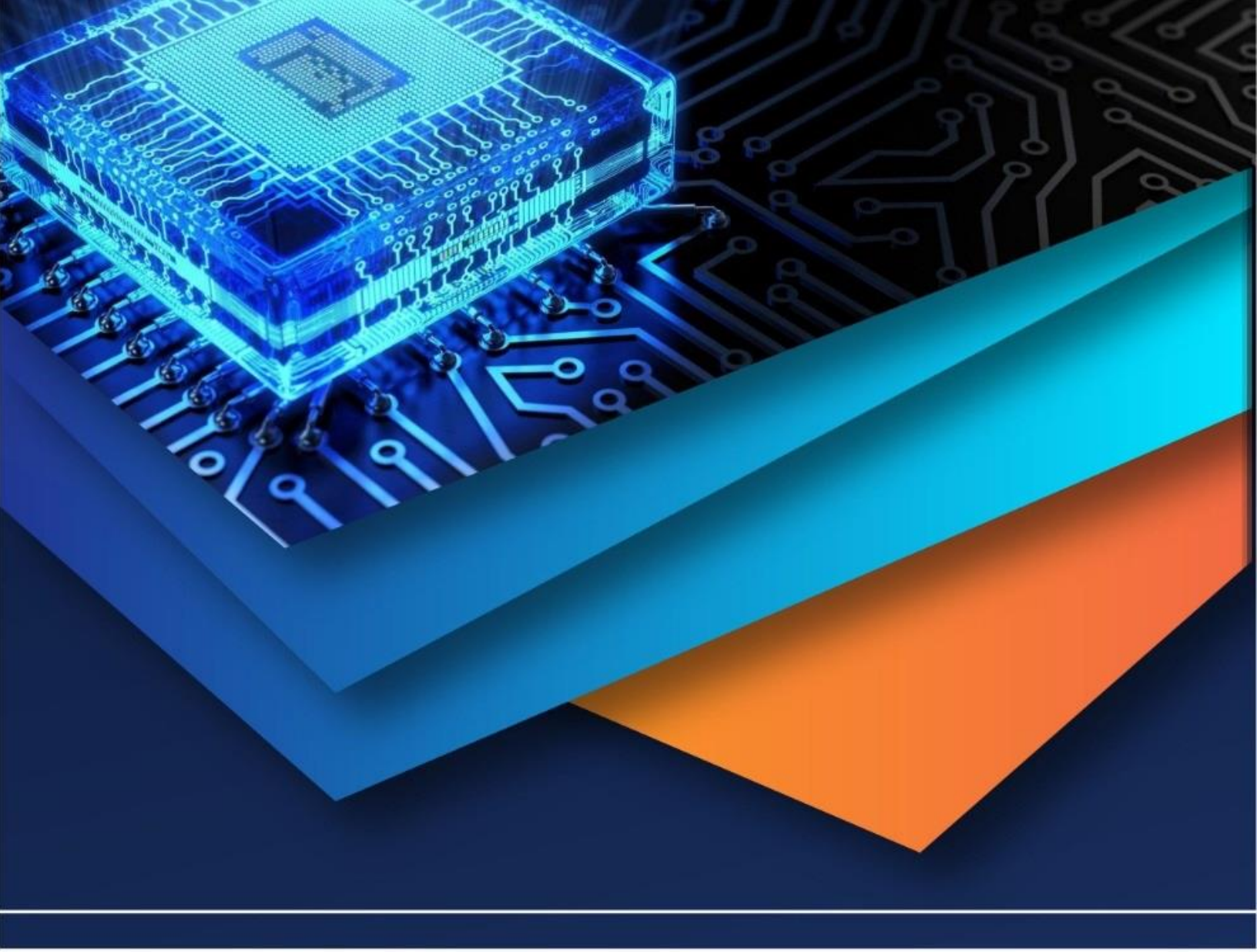
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