Diabetic Autonomic Neuropathy, a Co-factor related to Recurrent Urinary Tract Infections In Type2 Diabetic females, a Study in an Egyptian Population.

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Abstract: Bacterial infection is a common finding in diabetics presenting in outpatient clinics. It may occur in many organs, although urinary tract infection (UTI) is the most frequent. Women are significantly likely to develop UTI then men (1). Diabetic Autonomic Neuropathy (DAN) is a serious complication of diabetes (2). It is among the least recognized and understood complications despite its significant negative impact on survival (2,4). **Aim of Study:** The aim of our study is to correlate the occurrence of recurrent UTI with DAN in a female diabetic type2 population. **Materials & Methods:** We recruited 60 female patients suffering from recurrent UTI, age range from 30 – 50 years, diagnosed as type2 diabetes since a period of less than 5 years with average HbA1c of 7.5% range (7.2-8.1). All patients were subject to SudoScan test to diagnose DAN, Clinical examination and Laboratory assessment. **Results**: patients were categorized into three groups: group A: 20 patients suffering from mild DAN (40-50-uS) and mild UTI (pus cells 30-50 /HPF) - group B: 24 patients with moderate DAN (25-39 uS) and moderate UTI (pus cells 51-80 HPF) and (group C: 12 patients with severe DAN (< 25 uS) and severe UTI (pus cells > 100 /HPF). Culture & Sensitivity results demonstrated a variety of micro-organisms mainly *Escherichia coli*, *Staphylococcus saprophyticus, Klebsiella spp.*, *group B streptococcus and Candida albicans*. A combination of 2 to 3 antimicrobial agents was selected for every patient to be used for about 1-2 weeks. 28cases - half from every group - were randomly selected for adding anti-neuropathy agents. After 2 months, all patients presented for a second urine analysis, culture and HbA1c. The Results were as follow: 24 patients among the 28 selected for anti-neuropathy treatment showed negative results of culture & sensitivity compared to12 patients among the other 28 patients who received only antibiotic therapy (P<0.005). HbA1c decreased on average of 0.5%. **Conclusion**: These results along with the matching results of the Sudoscan prove the correlation between the presence of DAN and UTI and highlight its role as a co-factor with hyperglycemia in the pathogenesis of recurrent UTI.

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1. Introduction

Urinary tract infections (UTI) are considered to be the most common bacterial infection. According to the 1997 National Hospital Ambulatory Medical Care Survey, UTI accounted for nearly 7 million office visits and 1 million emergency department visits, resulting in 100 thousand hospitalizations. Furthermore, it is complicated by the fact that accurate diagnosis depends on both, symptoms and a positive urine culture (1).

Women are significantly likely to develop UTI than men (1,2). Nearly 1 in 3 women will have had at least one episode of UTI requiring antimicrobial therapy by the age of 24. UTI is usually classified by the site of infection: the bladder (cystitis), kidney (pyelonephritis), or urine (bacteriuria). It may be asymptomatic or symptomatic characterized by a wide spectrum of symptoms ranging from mild dysuria and difficult voiding to bacteremia, sepsis, or even death (3).

Diabetes increases the risk of UTI and bacteriuria mainly among female patients. Diabetic patients generally have a 2 to 4-fold increased incidence of UTI over non-diabetics (3,5).

The etiology of UTI among diabetic patients includes more unusual urine pathogens than UTI occurring among non-diabetic patients (5,6). UTI occurring in diabetic patients can lead to severe complications such as emphysematous cystitis and emphysematous pyelonephritis (6).

In Manitoba Canada, women with diabetes were up to 24 times more likely than nondiabetics to be hospitalized for pyelonephritis. Nondiabetic younger women (aged 25 - 44 years) were 4 times more likely than men- with similar age -to be hospitalized for pyelonephritis (7).

The financial implications of UTI are enormous, predominantly a result of the high incidence of the disease. Direct costs include the outpatient doctor visits, prescriptions, and hospitalization expenses, as well as the non-medical costs associated with travel, sick days, and morbidity. The indirect cost of lost output must also be considered (3,6).

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. DAN frequently coexists with other peripheral neuropathies and other diabetic complications. DAN may be present in different degrees, ranging from mild DAN or rather early stage to severe DAN or late stage. It may be detected early enough even before other more common diabetes complications (4,9).

Unfortunately, DAN is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes (4,9).

Furthermore, DAN can involve the entire autonomic nervous system (ANS). ANS vasomotor, viscero-motor and sensory fibers innervate every organ. DAN is also associated with genitourinary tract disturbances including bladder and /or sexual dysfunction (9).

Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent UTI, pyelonephritis, incontinence or a palpable bladder (9).

Many organs are dually innervated, receiving fibers from both the parasympathetic and sympathetic divisions of the ANS. Indeed, because the vagus nerve (the longest of the ANS nerves) accounts for about 75 % of all parasympathetic activities - and DAN manifests first in longer nerves - even early effects of DAN are widespread (10,11).

Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes, whereas symptoms suggestive of autonomic dysfunction may be common and frequently due to other causes rather than to true autonomic neuropathy. Subclinical autonomic dysfunction can occur within a year of diagnosing type 2 diabetes, and within 2 years in type1 diabetic patients. A fact that may explain many unusual clinical events in the diabetic population (12).

Aim of the Study

The aim of our study is to correlate the occurrence of recurrent UTI with DAN in a female diabetic type2 population, a fact that – if proven – can help the health care community to target this pathological subclinical condition as a possible underlying contributing factor of recurrent UTI in diabetic patients.

2. Material and Methods

We recruited 60 female patients suffering from recurrent UTI, age range from 30 – 50 years, BMI around 30, diagnosed as type2 diabetes since a period of less than 5 years with average HbA1c of 7.5% (range 7.2-8.1).

All patients were subject to SudoScan® test to diagnose DAN.This software device can detect clinical & subclinical DAN & peripheral neuropathy by the measurement of Electro-chemical Skin Conductance (ESC) of the hands and feet using two well-known principles: “reverse iontophoresis” and “electrochemistry”. ESC is expressed by micro-Siemens (uS) which is the ratio between the current generated and the constant direct voltage stimulus applied between the electrodes (< 4 V).

ESC evaluates local sudomotor function. It reflects the lesions of sympathetic nerve fibers that innervate sweat glands. These long and small unmyelinated fibers of the autonomic nervous system are the earliest nerve fibers to undergo damage in peripheral diabetic neuropathies.

Assessment of symmetry between right and left limbs is also important to differentiate diabetic peripheral neuropathy from other demyelinating neurological diseases or traumatic lesions.

http://www.impeto-medical.com/sudoscan-plus/about-sudoscan-plus/ (25).

All patients were subjected also to clinical examination and laboratory assessment including:

- Glycemic Profile (FBG-PPBG-HBA1c).
- Kidney Function Tests (urea-creatinine-uric-eGFR).
- Urine analysis with culture and sensitivity using Blood, MacConkey and CLED (Cysteine-Lactose-and Electrolyte-Deficient) agar.

NB. A clean-catch mid-stream morning urine sample collected from all patients.

- Complete Blood Count (CBC) and ESR.
- ALT & AST.

3. Results:

According to the Sudoscan reports, and the results of the urine analysis and culture, patients were categorized into three groups:

(Group A) 20 patients suffering from mild DAN (40-50-uS) and mild UTI (pus cells 30-50 /HPF)

(Group B) 24 patients with moderate DAN (25-39uS) and moderate UTI (pus cells 51-80 HPF) and

(Group C) 12 patients with severe DAN (< 25 uS) and severe UTI (pus cells > 100 /HPF) Fig.(1)

NB. The lower the current level of the Sudoscan report the more is the severity of DAN.

Only 4patients had severe DAN and mild UTI (pus cells 20 – 30/HPF), they received antibiotic therapy and were excluded from the study.

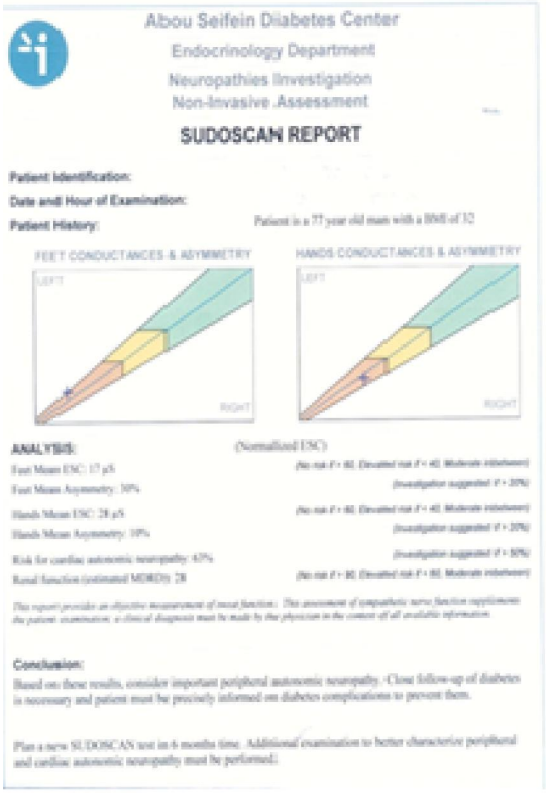

Figure (1): Sudoscan report showing severe DAN

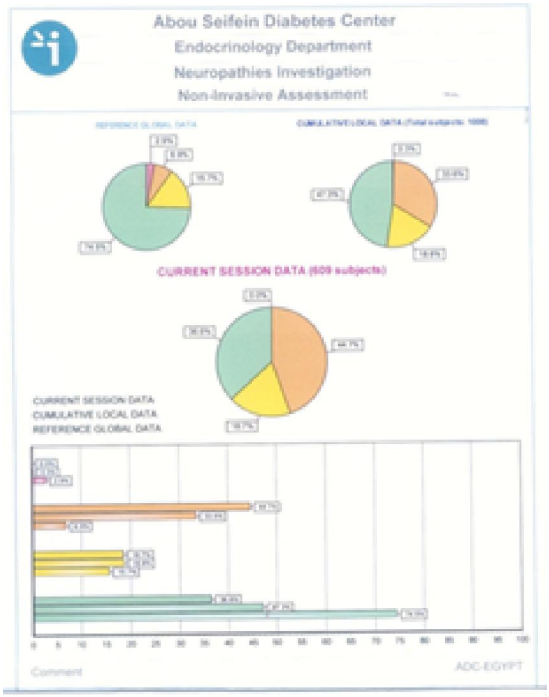

Figure (2): Cumulative Data

This correlation between the degree of DAN and the severity of UTI was highly significant (P<0.001).

All 56 included patients were on oral antidiabetic drugs with six patients on Basal/Oral regimen, the average matching HbA1c in the three groups was7.5% (range 7.2-8.1).

Culture and sensitivity results demonstrated a variety of micro-organisms mainly *Escherichia coli*, *Staphylococcus saprophyticus, Klebsiella spp.*, *group B Streptococcus and Candida albicans.*

Antibiotic therapy was prescribed using the culture and sensitivity results. A combination of 2 to 3 antimicrobial agents was selected for every patientto be used for about 1-2 weeks. A Fluoroquinolone was usually our first choice (Norfloxacin) together with Nitrofurantoin and in about half the patients a third agent Trimethoprim/Sulfamethoxazol was added or a third generation Cephalosporin. Five cases required the addition of Diflucan (fluconazole) 150 mg once.

28 cases, half from every group, were randomly selected for adding anti-neuropathy agents. For groupA, group B and group C, a neurotonic agent was prescribed (Oral Thioctic acid, 600 mg b.i.d) along with parentral Vitamin B complex (Becozyme IM /12 days) and for group C, a full course of a neurotrophic agent, Cerebrolysin® (a peptide with neuro-protective activity) was prescribed as well: 5 cc ampoule IM daily / 5 days/ week for 4 weeks.

After 2 months, all patients presented for a second CBC, urine analysis, culture & sensitivity and HbA1c. The Results were as follows:24 patients among the 28 selected cases for the anti-neuropathy treatment showed negative results for culture & sensitivity compared to only 12 patients among the other 28 cases who received only antibiotic therapy (P<0.005). HbA1c decreased on average of 0.5%.

These results along with the matching results of the Sudoscan prove the correlation between the presence of DAN and UTI and highlight its role as a co-factor with hyperglycemia in the pathogenesis of recurrent UTI.

Statistics

The statistic results are shown in Table 1 and Table 2.

Table (1) UTI & DAN

Source of variation	Sum of squares	Degree of freedom	Estimated v	F
Due to X1 residual	4.728 0.0005625	4 56	4.758 0.000047	995122.7
Total	4.7285625	60		

***P*< 0.001** (R2 95%)	Subtotal F at 0.005 level of significance = 3.4	R2 =0.95=95%

Rx1, y = -0.95 reflecting a highly significant correlation between DAN &UTI.

Table (2) UTI & NEURO THERAPY

		UTI/NEURO	UTI/ONLY	DIFF RATED	
Due to X1	2.6728	28 TOTAL	28 TOTAL	2.6728	
Residual	2.0857	24 NEG	12 NEG	0.017676	151.21
Total 28/28	4.7585	4 OUT 28	16 OUT 28	0.85714	
	***P*<0.05** R2				

4. Discussion

Predisposition to urinary tract infections (UTIs) in diabetes mellitus results from several factors. Susceptibility increases with longer duration and greater severity of diabetes (1). However, from our practice in a specialized diabetes center, UTI was always a challenge; from one point it is resistant to treatment and often relapses and from another point, it never shows up despite severe hyperglycemia.(13).

This confusing situation fueled our desire to find an explanation of why UTI is so common in some diabetic individuals and why it is recurrent in many cases.

Since the introduction of Sudoscan in our clinical practice, we noticed a relation between DAN and recurrent UTI in diabetic type2 female patients. This clinical observation along with the available data encouraged our team trying to unmask this possible relation.

From our cumulative data of 1008 cases (Fig.2) with this device, we concluded that this medical software (by Impeto medical) is a very useful non-invasive and accurate diagnostic tool for the early diagnosis of diabetic peripheral and autonomic neuropathy (4, 9, 13).

Complicated UTI in diabetic patients include renal and para-renal abscess, emphysematous pyelonephritis, emphysematous cystitis, fungal infections, xanthogranulomatous pyelonephritis, and papillary necrosis (17, 18, 20).

Emphysematous infection can involve one or all of three processes: emphysematous pyelonephritis is necrotizing infection of the body of the kidney that may spread to the para-renal areas, emphysematous pyelitis is limited to the collecting system and emphysematous cystitis to the bladder (15)(16)(20).

In our Study, the isolated organisms: *Escherichia coli*, *Staphylococcus saprophuticus, Klebsiella spp.*, and *Candida* are matching the results of other previous studies (21, 22).

Of course UTI is explained by many causative theories in diabetic patients: mainly glucosuria, hyperglycemia, female anatomy, immunocompromised individuals, cystopathy, nephropathy with ischemic kidneys and renal papillary necrosis, all are factors related to recurrent UTI in diabetic patients (22, 23). Vaginal candidiasis and vascular disease also play a role in recurrent infections (24).

However, as mentioned earlier, some patient lack almost all of these predisposing factors, and still are suffering from recurrent UTI - the same applies on recurrent skin infections in diabetic patients with near normal glycemic profile - a situation that raises many questions and inquiries and raises the possibility of a third party playing in the dark? Is it glycemic variability? Or is it a fake A1c? Or is it diabetic autonomic neuropathy? or all factors together?

Conclusion:

The results of our study are statistically significant and prove a correlation between the presence of DAN and UTI. Therapeutic intervention for DAN, along with antimicrobial agents seems effective in reducing the relapse rate of UTI and provides a better clinical outcome. However, further studies are recommended to evaluate the long-term effect of DAN when treating UTI and its impact among other chronic diabetes complications.

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